



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 18

A. R. Katritzky &
A. J. Boulton

Advances in
Heterocyclic
Chemistry

Volume 18

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

The present volume encompasses a wide range of heterocyclic chemistry. Syntheses of heterocycles from thioureas are reviewed by T. S. Griffin, T. S. Woods, and D. L. Klayman, while S. W. Schneller describes the chemistry of benzothiins and their derivatives (thiochromans, thiochromones, and thiochromanones). Developments in chrom-3-ene chemistry are reviewed by L. Merlini. F. D. Popp contributes a chapter on the isatins. A discussion of theoretical aspects of the tautomerism of pyrimidines, by J. S. Kwiatkowski and B. Pullman, follows up a corresponding earlier contribution (Vol. 13) on tautomeric purines. In the final chapter P. and D. Cagniant describe the natural occurrence and synthesis of the benzofurans.

A. R. KATRITZKY
A. J. BOULTON

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The Chemistry of Isatin

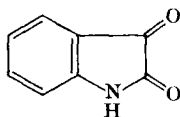
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I. Introduction

Isatin (1) was the subject of a comprehensive review, containing 416 references, by Sumpter in 1944.¹ Since that time an even larger number



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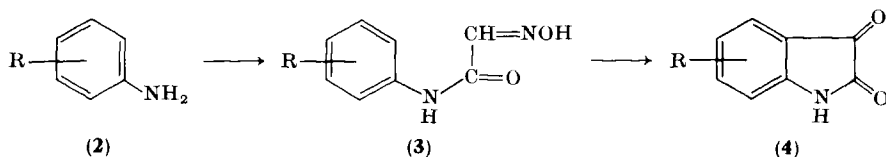
of papers have appeared concerning the preparation, properties, and reactions of isatin. Although isatin has been included as a small subtopic in several reviews concerned with indoles, no comprehensive review devoted to isatin has appeared since 1944.

It is the purpose of this review to cover the literature of isatin from the previous review¹ to late 1974. As far as possible it will adopt the same format as the earlier review, and materials that only updates subjects covered in depth in that review¹ will be listed, without extended comment.

II. Synthesis of Isatins

A. RING CLOSURE

The most frequently used synthesis of isatins is the Sandmeyer procedure, which involves the formation of an isonitrosoacetanilide (3) from an aniline (2), chloral hydrate, and hydroxylamine. The isonitroso-



acetanilide (3) is converted into the isatin (4) on treatment with sulfuric acid,¹ or less frequently polyphosphoric acid.²⁻⁵ Using the Sandmeyer

¹ W. C. Sumpter, *Chem. Rev.* **34**, 407 (1944).

² J. Gripenberg, E. Honkanen, and O. Patoharju, *Acta. Chem. Scand.* **11**, 1485 (1957).

³ F. Piozzi, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat. Rend.* **22**, 629 (1957).

⁴ F. Piozzi and G. Favini, *Atti Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat. Rend.* **18**, 647 (1955).

⁵ D. Răileanu and C. D. Nenitzescu, *Acad. Repub. Pop. Rom. Stud. Cercet. Chim.* **11**, 19 (1963).

reaction, *o*-substituted anilines have been converted into 7-alkyl,^{4,6-11} 7-methoxy,^{2,4} 7-nitro,¹² 7-amino,¹³ 7-carboxy,¹⁴ 7-trifluoromethyl,¹⁵ and 7-halo^{4,16-20} isatins. Similarly *p*-substituted anilines have been used to prepare 5-alkyl,^{4,6,8,9,21-23} 5-methoxy,^{4,24-28} 5-hydroxy,¹³ 5-trifluoromethyl,¹⁵ 5-carboxy,¹⁴ 5-carboxymethyl,²⁹ 5-amino,²⁷ 5-acetamido,³⁰ and 5-halo^{4,27,31,32} isatins.

Although *o*-bromo,⁴ *o*-chloro,^{4,16,17,20} and *o*-iodo¹⁷ anilines give 7-haloisatins, *o*-fluoroaniline has been reported³² not to give an isatin. 2,4-Difluoroaniline also fails to give an isatin³² although cyclization

- ⁶ F. Buscarons and J. M. Espinos, *Chim. Anal. (Paris)* **48**, 336 (1966).
⁷ N. P. Buu-Hoi and P. Jacquignon, *J. Chem. Soc.*, 3095 (1959).
⁸ H. Cassebaum, *J. Prakt. Chem.* **23**, 301 (1964).
⁹ A. L. Gershuns and A. A. Pavlyuk, *Ukr. Khim. Zh.* **30**, 1086 (1964); *Chem. Abstr.* **62**, 5252 (1965).
¹⁰ F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.* **93**, 1392 (1963).
¹¹ V. A. Snieckus, T. Onouchi, and V. Boekelheide, *J. Org. Chem.* **37**, 2845 (1972).
¹² E. R. Buchman, C. M. McCloskey, and J. A. Seneker, *J. Amer. Chem. Soc.* **69**, 380 (1947).
¹³ E. Giovannini, P. Portmann, A. Johl, K. Schnyder, B. Knecht, and H. P. Zen-Ruffinen, *Helv. Chim. Acta* **40**, 249 (1957).
¹⁴ P. N. Stefanescu, *Rev. Chim. (Bucharest)* **20**, 353 (1969).
¹⁵ P. M. Maginnity and C. A. Gaulin, *J. Amer. Chem. Soc.* **73**, 3579 (1951).
¹⁶ E. R. Buchman, H. Sargent, T. C. Myers, and J. A. Seneker, *J. Amer. Chem. Soc.* **68**, 2692 (1946).
¹⁷ M. B. Chaundhari and K. S. Nargund, *J. Univ. Bombay* **19**, Sect. A. Pt. 3, Sci. No. 28, 65 (1950); *Chem. Abstr.* **47**, 1652 (1953).
¹⁸ M. C. Chiang, C. Li, and J. L. Li, *Hua Hsueh Hsueh Pao* **22**, 235 (1956); *Chem. Abstr.* **52**, 10080 (1958).
¹⁹ P. W. Sadler and R. L. Warren, *J. Amer. Chem. Soc.* **78**, 1251 (1956).
²⁰ P. Singh, K. S. Dhami, G. M. Sharma, and K. S. Narang, *J. Sci. Ind. Res. Sect. B* **17**, 120 (1958).
²¹ N. P. Buu-Hoi and D. Guettier, *Bull. Soc. Chim. Fr.* 586 (1946).
²² N. P. Buu-Hoi, R. Royer, B. Eckert, and P. Jacquignon, *J. Chem. Soc.*, 4867 (1952).
²³ R. Ponci, T. Vitali, F. Mossini, and L. Amoretti, *Farmaco, Ed. Sci.* **22**, 999 (1967); *Chem. Abstr.* **68**, 114493 (1968).
²⁴ M. Akahoshi, *J. Pharm. Soc. Jap.* **71**, 710 (1951); *Chem. Abstr.* **46**, 2047 (1952).
²⁵ G. B. Bachman and G. M. Picha, *J. Amer. Chem. Soc.* **68**, 1599 (1946).
²⁶ M. F. Bartlett, D. F. Dickel, and W. I. Taylor, *J. Amer. Chem. Soc.* **80**, 126 (1958).
²⁷ M. Cirje, *Rev. Roum. Chim.* **18**, 1013 (1973).
²⁸ S. Pietra, *Farmaco (Pavia), Ed. Sci.* **13**, 75 (1958); *Chem. Abstr.* **52**, 13704 (1958).
²⁹ D. J. Bauer and P. W. Sadler, *Brit. J. Pharmacol.* **15**, 101 (1960).
³⁰ A. Ermili and R. Giuliano, *Gazz. Chim. Ital.* **89**, 517 (1959).
³¹ R. N. Castle, K. Adachi, and W. D. Guither, *J. Heterocycl. Chem.* **2**, 459 (1965).
³² V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.* **23**, 1858 (1958).

does occur when *p*-fluoroaniline^{31,32} and 3,4-difluoroaniline³² are used.

Generally meta-substituted anilines give rise to a mixture of 4- and 6-substituted isatins^{9,13,19,33-37} although 4-trifluoromethyl,^{15,33,35,38} 4-nitro,¹³ 4-amino,¹³ 4-hydroxy,¹³ 4-carboxy,¹³ 6-methoxy,³⁵ and 6-bromo⁴ isatins have been reported without the other isomer.

The Sandmeyer method has been used with di- and trisubstituted anilines to prepare di-^{4,6,13,14,19,32,38-55} and tri-^{5,13,19,30,56} substituted isatins. Although *p*-acetamidoaniline and 5-acetamido-2-aminotoluene gave 5-acetamido- and 5-acetamido-7-methylisatin, respectively,³⁰ the use of 4-acetamido-2-aminotoluene and 5-acetamido-2,4-dimethylaniline gave the appropriate aminoisatins.^{30,52} Other examples of hydrolysis during this cyclization are in the conversion of diethyl 5-aminoisophthalate to isatin-4,6-dicarboxylic acid⁵³ and 2-methyl-5-

³³ B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 164 (1952).

³⁴ A. Mangini and R. Passerini, *Gazz. Chim. Ital.* **85**, 840 (1955).

³⁵ P. W. Sadler, *J. Org. Chem.* **21**, 169 (1956).

³⁶ A. E. Senear, H. Sargent, J. F. Mead, and J. B. Koepfli, *J. Amer. Chem. Soc.* **68**, 2695 (1946).

³⁷ H. Wexler, *Acad. Repub. Pop. Romine, Filiala Iasi, Stud. Cercet. Stiint., Chim.* **12**, 219 (1961); *Chem. Abstr.* **58**, 3379 (1963).

³⁸ B. R. Baker and R. E. Schaub, British Patent 713,767 (1954); *Chem. Abstr.* **50**, 14002 (1956).

³⁹ B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 157 (1952).

⁴⁰ B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.* **17**, 149 (1952).

⁴¹ E. Bullock and A. W. Johnson, *J. Chem. Soc.*, 1602 (1957).

⁴² F. Buscarons and L. S. Moreno, *Inform. Quim. Anal.* **21**, 191 (1967).

⁴³ N. P. Buu-Hoi, B. Eckert, and R. Royer, *C.R. Acad. Sci.* **232**, 1356 (1951).

⁴⁴ H. Cassebaum and K. Liedel, *J. Prakt. Chem.* **12**, 91 (1960).

⁴⁵ A. Ermili and R. Giuliano, *Gazz. Chim. Ital.* **89**, 517 (1959).

⁴⁶ S. Gronowitz and G. Hansen, *Ark. Kemi* **27**, 145 (1967).

⁴⁷ M. Hashimoto and K. Hattori, *Chem. Pharm. Bull.* **14**, 1314 (1966).

⁴⁸ R. Hodges, J. W. Ronaldson, A. Taylor, and E. P. White, *J. Chem. Soc.*, 5332 (1963).

⁴⁹ H. B. MacPhillamy, R. L. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Amer. Chem. Soc.* **80**, 2172 (1958).

⁵⁰ F. G. Mann and J. H. Turnbull, *J. Chem. Soc.*, 747 (1951).

⁵¹ H. Mix, *Justus Liebigs Ann. Chem.* **592**, 146 (1955).

⁵² H. Mix and H. W. Krause, *Chem. Ber.* **89**, 2630 (1956).

⁵³ H. Mix, H. W. Krause, and J. Reihsig, *J. Prakt. Chem.* **6**, 174 (1958).

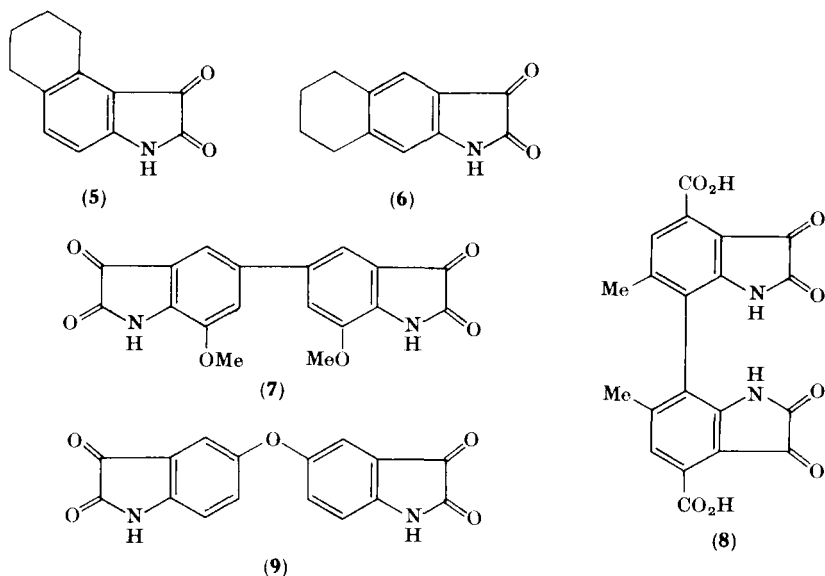
⁵⁴ Y. Omote, H. Tazawa, Y. Fujinuma, and N. Sugiyama, *Bull. Chem. Soc. Jap.* **42**, 3016 (1969).

⁵⁵ H. Wexler and A. Caraculacu, *An. Stiint. Univ. "A. T. Cuza," Iasi, Sect. IC* **13**, 71 (1967); *Chem. Abstr.* **69**, 106525 (1968).

⁵⁶ R. Hodges and A. Taylor, *J. Chem. Soc.*, 4310 (1964).

cyanoaniline to 7-methylisatin-4-carboxamide.⁵² An *N*-methyl analog of **3** has been converted into an *N*-methylisatin.^{57,58}

Use of the appropriate tetrahydronaphthylamine has led to fused isatins such as **5** and **6**,⁴⁰ while diaminobiphenyls have given rise to



compounds of the type **7**¹⁴ and **8**.⁵¹ 4,4'-Diaminodiphenylether led to the isatin **9**.⁵⁹ A number of *m*-phenylenediamines have been subjected to this sequence. Thus while *m*-phenylenediamine and 2,6-diaminotoluene gave **10** and **11** respectively,⁶⁰ 2,4-diaminochlorobenzene gives **12**.⁶¹ Finally, 2,4-diaminotoluene gives rise to **13** which has been postulated to arise in the alkali workup of **14**.⁶¹

ω -Nitroacetanilide and sulfuric acid or hydrofluoric acid gave a good yield of isatin-3-oxime.⁶² It is assumed that the cyclization took place via PhNHCOC(OH)=NOH .

Treatment of anilines with oxalyl chloride followed by cyclization of the intermediate **15** is a useful isatin synthesis. Generally a Lewis acid

⁵⁷ F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.* **23**, 19 (1958).

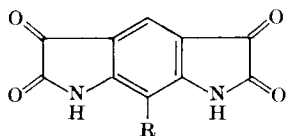
⁵⁸ J. M. Z. Gladych and J. H. Hunt, S. African Patent 68 04,428 (1968); *Chem. Abstr.* **71**, 81436 (1969).

⁵⁹ I. Shopov, *Dokl. Bolg. Akad. Nauk* **21**, 241 (1968); *Chem. Abstr.* **69**, 3207 (1968).

⁶⁰ Z. J. Allan, *Chem. Listy* **46**, 228 (1952).

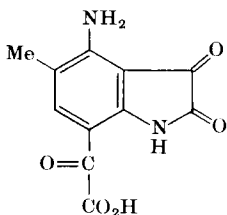
⁶¹ Z. J. Allan, *Chem. Listy* **46**, 224 (1952).

⁶² K. Wiechert, H. H. Heilmann, and W. Jacob, *Z. Chem.* **1**, 191 (1961).

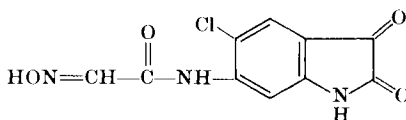


(10) R = H

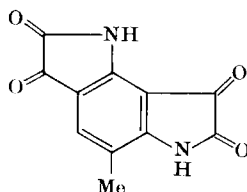
(11) R = Me



(13)

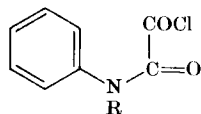


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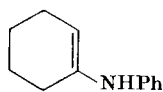


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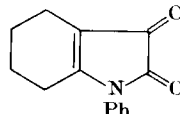
is used for the cyclization,^{58,63-74} but in some cases, for example 3,5-dimethoxyaniline,⁷⁵ no Lewis acid is needed. With 2,3-dichlorodiphenylamine, cyclization takes place onto the unsubstituted ring to give *N*-(2,3-dichlorophenyl)isatin.⁷⁴ This method has also been applied to the synthesis of tetrahydroisatins.^{76,77} Thus **16** and oxalyl chloride gave



(15)



(16)



(17)

⁶³ H. E. Baumgarten and J. L. Furnas, *J. Org. Chem.* **26**, 1536 (1961).

⁶⁴ J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 3904 (1952).

⁶⁵ J. W. Cusic and W. E. Coyne, U.S. Patent 3,509,149 (1970); *Chem. Abstr.* **73**, 3931 (1970).

⁶⁶ A. DaSettimo and E. Nannipieri, *J. Org. Chem.* **35**, 2546 (1970).

⁶⁷ B. A. Hess and S. Corbino, *J. Heterocycl. Chem.* **8**, 161 (1971).

⁶⁸ H. S. Lowrie, U.S. Patent 3,265,693 (1966); *Chem. Abstr.* **65**, 15395 (1966).

⁶⁹ H. S. Lowrie, U. S. Patent 3,297,694 (1967); *Chem. Abstr.* **66**, 76020 (1967).

⁷⁰ H. S. Lowrie, *J. Med. Chem.* **9**, 664 (1966).

⁷¹ M. S. Newman and W. H. Powell, *J. Org. Chem.* **26**, 812 (1961).

⁷² A. Sallmann and R. Pfister, German Patent 1,815,802 (1969); *Chem. Abstr.* **72**, 12385 (1970).

⁷³ A. Sallmann and R. Pfister, German Patent 1,815,807 (1969); *Chem. Abstr.* **71**, 101552 (1969).

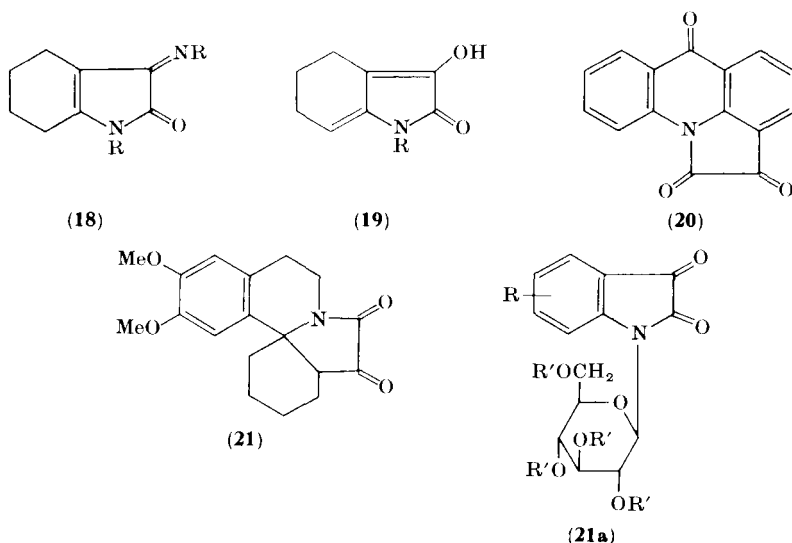
⁷⁴ R. A. Scherrer, U.S. Patent 3,238,201 (1966); *Chem. Abstr.* **64**, 17614 (1966).

⁷⁵ H. Newman and R. B. Angier, *J. Org. Chem.* **34**, 3484 (1947).

⁷⁶ E. Ziegler, M. Eder, K. Belegtratis, and E. Prewedourakis, *Monatsh. Chem.* **98**, 2249 (1967).

⁷⁷ E. Ziegler, F. Hradetzky, and M. Eder, *Monatsh. Chem.* **97**, 1391 (1966).

what was reported as **17**.⁷⁷ Reaction of cyclohexanone and dimethyl-oxalate gives a substituted glyoxylic ester which reacts with amines to form anils (**18**) which on acid hydrolysis give rise to similar compounds.⁷⁸⁻⁸⁰ Use of guanidine or urea as the amine with 2-oxocyclohexylglyoxylic acid gave quinazoline derivatives rather than **19**.⁸¹ Infrared^{79,80}



and NMR⁸¹ studies support the tautomeric structure **19** for these so-called tetrahydroisatins. The isatin derivative **20** was obtained from acridone by oxalate cyclization.⁶⁷ The half ester-half acid chloride of oxalic acid has also been used in this synthesis.⁸² The ester of 2-oxocyclohexylglyoxylic acid and 3,4-dimethoxyphenethylamine gave **18** (R = 3,4-dimethoxyphenylethyl)⁸³⁻⁸⁶ which on treatment with phosphoric acid gave the hexahydroisatin derivative **21**. 3-Acetoxy-2,4,5,6-tetrahydro-2-oxobenzofuran and ammonia, ethylamine, or aniline gave **19** (R = H, Et, or Ph, respectively).⁸⁷ 1- β -D-Glucopyranosides of isatins (**21a**) were

⁷⁸ L. Horwitz, *J. Amer. Chem. Soc.* **75**, 4060 (1953).

⁷⁹ D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 876 (1959).

⁸⁰ R. J. S. Beer and J. Hollowood, *J. Chem. Soc.*, 991 (1964).

⁸¹ W. L. F. Armarego and B. A. Milloy, *J. Chem. Soc., Perkin Trans. 1*, 2814 (1973).

⁸² L. Baiocchi, *Ann. Chim. (Rome)* **57**, 492 (1967).

⁸³ A. Mondon, German Patent 1,105,424 (1957); *Chem. Abstr.* **56**, 7284 (1962).

⁸⁴ A. Mondon, *Justus Liebigs Ann. Chem.* **628**, 123 (1959).

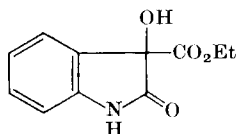
⁸⁵ A. Mondon and H. Witt, *Chem. Ber.* **103**, 1522 (1970).

⁸⁶ A. Mondon, K. F. Hansen, K. Boehme, H. P. Faro, H. J. Nestler, H. G. Vilhuber, and K. Bottcher, *Chem. Ber.* **103**, 615 (1970).

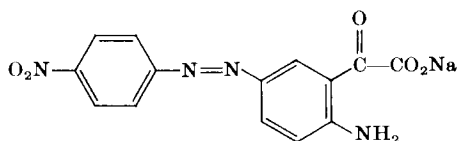
⁸⁷ R. J. S. Beer and R. W. Turner, *J. Chem. Soc.*, 1648 (1965).

prepared by condensation of the appropriate glucopyranosyl aniline derivatives with oxalyl chloride.^{87a}

The Martinet reaction is a somewhat similar method that makes use of the reaction of an aniline and oxomalonate ester to give **22**, which on



(22)

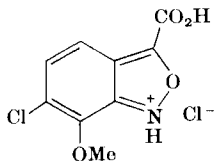


(23)

treatment with alkali in the presence of oxygen gives an isatin via a dioxindole.⁸⁸⁻⁹⁷

Treatment of potassium isatin with sodium formate in acetic-formic anhydride gave 1-formylisatin,⁹⁸ while the sodium isatin **23** was cyclized by treatment with acid to the expected 5-substituted isatin.⁹⁹

o-Nitrobenzoyldiazomethanes have been cyclized by acid to *N*-hydroxyisatins.^{100,101} Use of a ¹⁴C label in the diazo carbon led to an isatin with all of the ¹⁴C in the 2-position; the mechanism of this



(24)

^{87a} M. N. Preobrazhenskaya, I. V. Yartseva, and L. V. Ektova, *Dokl. Acad. Nauk SSSR* **215**, 873 (1974).

⁸⁸ W. T. Colwell, J. K. Horner, and N. A. Skinner, *U.S. Dep. Com., Office Tech. Serv. AD 435,889* (1964); *Chem. Abstr.* **62**, 11763 (1965).

⁸⁹ W. Langenbeck, K. Ruhlmann, H. H. Reif, and F. Stolze, *J. Prakt. Chem.* **4**, 136 (1957).

⁹⁰ A. Martinet, *C.R. Acad. Sci.* **242**, 2358 (1956).

⁹¹ J. R. Merchant and S. S. Salgar, *J. Indian Chem. Soc.* **40**, 23 (1963).

⁹² R. E. Schachat, E. I. Becker, and A. D. McLaren, *J. Org. Chem.* **16**, 1349 (1951).

⁹³ F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.* **20**, 1454 (1955).

⁹⁴ V. H. Brown, W. A. Skinner, and J. I. DeGraw, *J. Heterocycl. Chem.* **6**, 539 (1969).

⁹⁵ N. P. Buu-Hoi, P. Jacquignon, and E. Allegrini, *J. Chem. Soc.*, 4836 (1961).

⁹⁶ H. Cassebaum, *Chem. Ber.* **90**, 2876 (1957).

⁹⁷ J. W. Clark-Lewis and J. A. Edgar, *J. Chem. Soc.*, 5551 (1965).

⁹⁸ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. B*, 449 (1967).

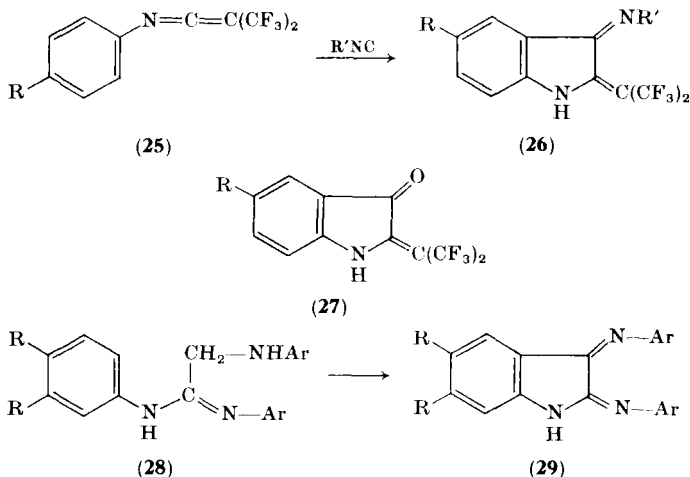
⁹⁹ J. Jarkovsky and Z. J. Allan, *Collect. Czech. Chem. Commun.* **26**, 2940 (1961).

¹⁰⁰ E. Giovannini and P. Portmann, *Helv. Chim. Acta* **31**, 1381 (1948).

¹⁰¹ E. C. Taylor and D. R. Eckroth, *Tetrahedron* **20**, 2059 (1964).

conversion has been discussed.¹⁰¹ Treatment of **24** with ammonium hydroxide followed by ferrous sulfate gave 6-chloro-7-methoxyisatin.¹⁰²

A number of ring closures have been reported that lead to 2- or 3-substituted isatins. Thus, treatment of nitromalonbis-*N*-methylanilide with acid gives *N*-methyilisatin-3-oxime.¹⁰³ Reaction of **25** with cyclohexyl or *t*-butylisocyanide gives **26**, which was hydrolyzed by acid to **27**.¹⁰⁴ Heating of **28** gives, with oxidation, the isatin-2,3-dianil **29**.¹⁰⁵



B. RING CONTRACTIONS

A number of so-called 2,4-dihydroxyquinolines, after the introduction of a 3-hydroxyimino,¹⁰⁶ 3-nitroso,^{107,108} 3-hydroxy-3-amino,¹⁰⁹ or more frequently 3,3-dihalo groups,¹¹⁰⁻¹¹⁴ give isatins with sulfuric acid or sodium hydroxide. Treatment with sodium hydroxide of 3,3-

¹⁰² D. R. Eckroth, T. G. Cochran, and E. C. Taylor, *J. Org. Chem.* **31**, 1303 (1966).

¹⁰³ J. W. Clark-Lewis and G. F. Katekar, *J. Chem. Soc.*, 2825 (1959).

¹⁰⁴ D. P. Deltsova, E. A. Avetisyan, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 355 (1973); *Chem. Abstr.* **78**, 147724 (1973).

¹⁰⁵ E. Ziegler, W. Kaufmann, and W. Klementschtz, *Monatsh. Chem.* **83**, 1334 (1952).

¹⁰⁶ R. Hardman and M. W. Partridge, *J. Chem. Soc.*, 614 (1958).

¹⁰⁷ F. N. Lahey, J. A. Lamberton, and J. R. Price, *Aust. J. Sci. Res. Ser. A* **3**, 155 (1950).

¹⁰⁸ J. A. Lamberton and J. R. Price, *Aust. J. Chem.* **6**, 173 (1953).

¹⁰⁹ T. Kappe, E. Lender, and E. Ziegler, *Monatsh. Chem.* **99**, 2157 (1968).

¹¹⁰ E. Ziegler and T. Kappe, *Monatsh. Chem.* **94**, 698 (1963).

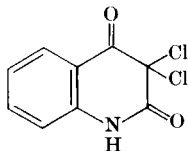
¹¹¹ E. Ziegler and T. Kappe, *Monatsh. Chem.* **94**, 736 (1963).

¹¹² E. Ziegler, T. Kappe, and R. Salvador, *Monatsh. Chem.* **94**, 453 (1963).

¹¹³ E. Ziegler, R. Salvador, and T. Kappe, *Monatsh. Chem.* **94**, 941 (1963).

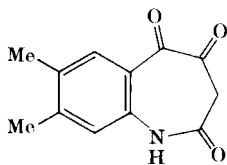
¹¹⁴ E. Ziegler, R. Wolf, and T. Kappe, *Monatsh. Chem.* **96**, 418 (1965).

dichloro-2,4-dioxo-1,2,3,4-tetrahydroquinoline (**30**) labeled at carbon 3 with ^{14}C resulted in 100% loss of the activity as $^{14}\text{CO}_2$ and gave isatin which contained no ^{14}C .¹¹⁵



(30)

7-Methoxy-2-methyl-1,4-dihydro-4-oxoquinoline was converted into 6-methoxyisatin by an oxidative ring opening followed by ring closure.^{115a} Oxidation of 4-methyl-*N*-(2,3-dimethylphenyl)-carbostyryl with alkaline permanganate gave *N*-(2,3-dimethylphenyl)isatin.⁷⁴



(31)

Treatment of **31** with alkali gave 5,6-dimethylisatin in addition to a quinoline derivative.¹¹⁶

C. FROM INDOLE DERIVATIVES

Chromic acid oxidation of a variety of indoles has been used as a synthetic route to isatins.¹¹⁷⁻¹²⁴ A variety of other oxidative methods

¹¹⁵ T. Kappe, Personal Communication, 1973.

^{115a} W. Salzer, H. Timmler, and H. Andersag, *Ber.* **81**, 12 (1948).

¹¹⁶ A. H. Rees, *J. Chem. Soc.*, 311 (1959).

¹¹⁷ A. DaSettimo, M. F. Saettone, E. Nannipieri, and P. Barili, *Gazz. Chim. Ital.* **97**, 1304 (1967).

¹¹⁸ E. Kambli, *Helv. Chim. Acta* **47**, 2155 (1964).

¹¹⁹ M. Kunori, *Nippon Kagaku Zasshi* **81**, 1431 (1960).

¹²⁰ W. E. Noland and R. D. Rieke, *J. Org. Chem.* **27**, 2250 (1962).

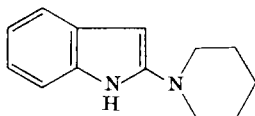
¹²¹ W. E. Noland and K. R. Rush, *J. Org. Chem.* **29**, 947 (1964).

¹²² A. P. Terentev and M. N. Preobrazhenskaya, *Dokl. Akad. Nauk.SSSR* **118**, 302 (1958); *Chem. Abstr.* **52**, 11003 (1958).

¹²³ A. P. Terentev and M. N. Preobrazhenskaya, *Zh. Obshchei Khim.* **29**, 317 (1959); *Chem. Abstr.* **53**, 21874 (1959).

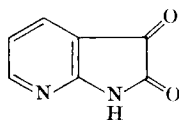
¹²⁴ A. P. Terentev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *Zh. Obshchei Khim.* **29**, 2541 (1959); *Chem. Abstr.* **54**, 10991 (1960).

have also been employed.^{64,66,74,125-135a} Thus, for example, treatment of **32** with oxygen in triethylamine gave isatin.¹³³ Various *N,N'*-dialkylated indigo dyes have been oxidized with nitric acid to *N*-alkylisatins.¹³⁴ Oxidation of sporidesmin, a mold metabolic product, gave 5-chloro-6,7-dimethoxy-1-methylisatin.¹³⁵

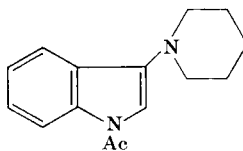


(32)

Dihalogenation of oxindole followed by alkaline hydrolysis of the 3,3-dihalo-oxindole has been applied to the synthesis of some isatins.^{66,126,136-137b} A number of oxindoles have been treated with nitrous acid to give isatin-3-oximes.^{100,138} Reduction of the oximes to 3-aminoxindoles followed by ferric chloride oxidation gave isatins.^{100,138} When this sequence was applied to 7-azaoxindole, the azaisatin **33** was



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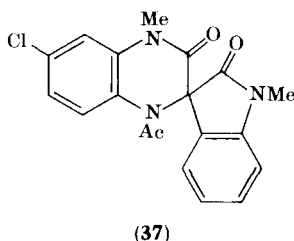
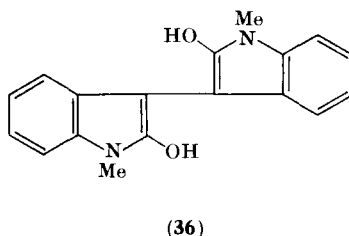
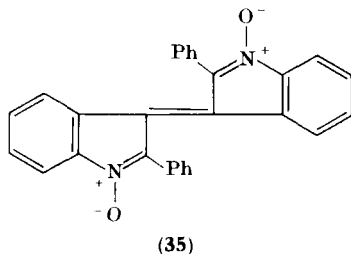


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- ¹²⁵ G. Berti, A. DaSettimo, and O. Livi, *Tetrahedron* **20**, 1397 (1964).
¹²⁶ E. Giovannini and P. Portmann, *Helv. Chim. Acta* **31**, 1375 (1948).
¹²⁷ T. Lesiak, *Rocz. Chem.* **37**, 347 (1963); *Chem. Abstr.* **59**, 6342 (1963).
¹²⁸ O. Neunhoeffer and G. Lehmann, *Chem. Ber.* **94**, 2965 (1961).
¹²⁹ A. Romeo, H. Corrodi, and E. Hardegger, *Helv. Chim. Acta* **38**, 463 (1955).
¹³⁰ S. K. Saha, *J. Indian Chem. Soc., Ind. News Ed.* **13**, 178 (1950); *Chem. Abstr.* **45**, 8004 (1951).
¹³¹ T. Sato and M. Ohto, *Bull. Chem. Soc. Jap.* **28**, 480 (1955); *Chem. Abstr.* **50**, 12018 (1956).
¹³² R. A. Scherrer, Belgian Patent 637,515 (1964); *Chem. Abstr.* **63**, 4307 (1965).
¹³³ T. Hino, M. Nakagawa, T. Hashizume, N. Yamaji, Y. Miwa, K. Tsuneoka, and S. Akaboshi, *Tetrahedron* **27**, 775 (1971).
¹³⁴ R. Pummerer and F. Meininger, *Justus Liebigs Ann. Chem.* **590**, 173 (1954).
¹³⁵ R. Hodges, J. W. Ronaldson, A. Taylor, and E. P. White, *Chem. Ind. (London)*, 42 (1963).
^{135a} R. Hodges, J. W. Ronaldson, J. S. Shannon, A. Taylor, and E. P. White, *J. Chem. Soc.*, 26 (1964).
¹³⁶ R. J. Bass, *Tetrahedron* **27**, 3263 (1971).
¹³⁷ L. Simet, *J. Org. Chem.* **28**, 3580 (1963).
^{137a} T. A. Foglia and D. Swern, *J. Org. Chem.* **33**, 4440 (1968).
^{137b} A. DaSettimo, C. Menicagli, and E. Nannipier, *J. Org. Chem.* **39**, 1995 (1974).
¹³⁸ E. Giovannini and P. Portmann, *Helv. Chim. Acta* **31**, 1392 (1948).

obtained.¹³⁹ This appears to be the only report in the literature of an azaisatin. Reaction of *N*-acetyloxindolyl¹⁴⁰ and **34**¹⁴¹ with nitrous acid gave *N*-acetylisatin-2-oxime. A similar reaction takes place with indoxyl.¹⁴⁰

Heating of *N*-methyloxindole and **35** in toluene gives **36** and *N*-methylisatin.¹⁴² In a similar manner isatin was obtained from oxindole.¹⁴² The mechanism of these transformations has been discussed. The



spiroindole **37** has been converted to *N*-methylisatin and a number of other products.¹⁰³

III. N-Substituted Isatins

A. PREPARATION FROM ISATIN

Isatin sodium or potassium salts react with dimethyl^{34,58,143-146} and diethyl¹⁴⁷ sulfate, a variety of alkyl halides,^{11,48,54,148-162} acyl

¹³⁹ H. Kagi, *Helv. Chim. Acta* **24**, 141E (1941).

¹⁴⁰ A. Etienne, *Bull. Soc. Chim. Fr.*, 651 (1948).

¹⁴¹ D. Răileanu, V. Daniel, E. Mosanu, and C. D. Nenitzescu, *Rev. Roum. Chim.* **12**, 1367 (1967).

¹⁴² P. Bruni and M. Poloni, *Gazz. Chim. Ital.* **100**, 1119 (1970).

¹⁴³ J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, K. Clarke, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, 2222 (1957).

¹⁴⁴ R. C. Elderfield and H. H. Rembges, *J. Org. Chem.* **32**, 3809 (1967).

¹⁴⁵ S. Pietra and G. Tacconi, *Farmaco (Pavia), Ed. Sci.* **14**, 854 (1959).

¹⁴⁶ N. M. Turkevich and O. F. Lyman, *Metody Poluch. Khim. Reaktivov Prep.*, 117 (1971); *Chem. Abstr.* **78**, 4063 (1973).

¹⁴⁷ C. B. Hudson and A. V. Robertson, *Aust. J. Chem.* **20**, 1521 (1967).

halides,^{152,153,163-166} and anhydrides^{32,167,168} to give *N*-alkyl and *N*-acylisatins. Silver salts of isatin have also been used to prepare *N*-alkylisatins.^{148,149} In a similar manner 5-methylisatin and acrylonitrile

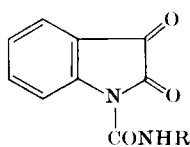


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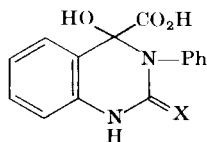
with Triton B gave **38**.^{169,170} Ketene has seen limited use in the preparation of *N*-acetylisatins.¹⁷¹ When heated in water gramine and isatin gave *N*-skatylisatin.¹⁷²

- ¹⁴⁸ A. E. Arbuzov and M. S. Bastanova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 459 (1952); *Chem. Abstr.* **47**, 4876 (1953).
¹⁴⁹ A. E. Arbuzov and O. M. Shapshinskaya, *Tr. Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova*, No. **16**, 11 (1951); *Chem. Abstr.* **51**, 12065 (1957).
¹⁵⁰ R. L. Autrey and F. C. Tahk, *Tetrahedron* **23**, 901 (1967).
¹⁵¹ D. J. Bauer and P. W. Sadler, British Patent 1,026,401 (1966); *Chem. Abstr.* **65**, 2224 (1966).
¹⁵² N. Hirose, S. Sohda, and S. Toyoshima, *Yakugaku Zasshi* **91**, 1323 (1971).
¹⁵³ R. Kikumoto and T. Kobayashi, *Tetrahedron* **22**, 3337 (1966).
¹⁵⁴ F. Knotz, *Sci. Pharm.* **38**, 20 (1970).
¹⁵⁵ F. Knotz, *Sci. Pharm.* **38**, 98 (1970).
¹⁵⁶ F. Knotz, *Sci. Pharm.* **38**, 163 (1970).
¹⁵⁷ R. G. Johnston and D. Kidd, *J. Chem. Soc.*, 4734 (1964).
¹⁵⁸ P. Lakshminarayana, K. K. Balasubramanian, and P. Shanmugam, *J. Chem. Soc. Perkin Trans. 1*, 998 (1973).
¹⁵⁹ A. Lindquist, P. Lagerstrom, and R. Dahlbom, *Acta Pharm. Suecica* **9**, 93 (1972).
¹⁶⁰ J. Plostnieks, U.S. Patent 3,428,649 (1969); *Chem. Abstr.* **70**, 68150 (1969).
¹⁶¹ H. Schafer, *Arch. Pharm.* **303**, 183 (1970).
¹⁶² G. Tacconi, P. P. Righetti, and G. Desimoni, *J. Prakt. Chem.* **315**, 339 (1973).
¹⁶³ E. H. Huntress and J. Bornstein, *J. Amer. Chem. Soc.* **71**, 745 (1949).
¹⁶⁴ R. Pater, *J. Heterocycl. Chem.* **7**, 1113 (1970).
¹⁶⁵ J. M. Muchowski, *Can. J. Chem.* **48**, 1946 (1970).
¹⁶⁶ C. Runti and F. Collino, *Farmaco, Ed. Sci.* **24**, 577 (1969).
¹⁶⁷ S. J. Holt, A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 1217 (1958).
¹⁶⁸ R. E. Lyle, D. E. Portlock, M. J. Kane, and J. A. Bristol, *J. Org. Chem.* **37**, 3967 (1972).
¹⁶⁹ F. J. DiCarlo and H. G. Lindwall, *J. Amer. Chem. Soc.* **67**, 199 (1945).
¹⁷⁰ D. Waite, *J. Chem. Soc. C*, 550 (1970).
¹⁷¹ Y. V. Svetkin, *Zh. Obshchei Khim.* **26**, 1216 (1956); *Chem. Abstr.* **50**, 16703 (1956).
¹⁷² A. Kamal, M. Anjum, and S. Aziz, *Pak. J. Sci. Ind. Res.* **9**, 323 (1966); *Chem. Abstr.* **71**, 3199 (1969).

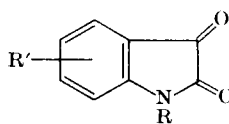
Isatin and triethylamine with methyl and phenylisocyanate has been reported to give **39** (R = Me and Ph, respectively).¹⁷³ In alkali, however, isatin and phenylisocyanate or phenylisothiocyanate gave the quinazolines **40** (X = O or S).¹⁷⁴ Base-catalyzed reactions of isatins and ClSCFCl_2 ,¹⁷⁵ Cl_3CSH ,¹⁷⁶ and Cl_3CSCl ¹⁷⁷⁻¹⁷⁹ gave **41** (R = SCFCl_2 and SCCl_3 , respectively), and reaction of isatin with dimethylsulfoxide in acetic acid gave **41** (R = CH_2SMe_3).¹⁸⁰



(39)



(40)



(41)

Isatin reacts with formaldehyde and a variety of amines in the Mannich reaction to give compounds of type **42**.^{181-193a} A similar reaction takes place with isatin-3-thiosemicarbazone,^{185,187} or **42** can react with thiosemicarbazide to give a similar product.¹⁹² In the absence of an amine, isatin¹⁸¹ and substituted isatins^{157,193a} with form-

¹⁷³ L. Capuano and M. Welter, *Chem. Ber.* **101**, 3671 (1968).

¹⁷⁴ P. Gyulai and K. Lempert, *Period. Polytech. Chem. Eng.* **14**, 13 (1970).

¹⁷⁵ E. Kuehle, E. Klauke, F. Grewe, and H. Kaspers, Belgian Patent 621,711 (1963); *Chem. Abstr.* **59**, 11510 (1963).

¹⁷⁶ R. Aries, French Patent 1,492,948 (1967); *Chem. Abstr.* **69**, 59240 (1968).

¹⁷⁷ Chimetron S.a.r.l., Belgian Patent 696,711 (1967); *Chem. Abstr.* **71**, 101891 (1969).

¹⁷⁸ C. Hennart, *Bull. Soc. Chim. Fr.*, 2968 (1967).

¹⁷⁹ C. Hennart, French Patent 1,497,492 (1967); *Chem. Abstr.* **69**, 106555 (1968).

¹⁸⁰ H. H. Otto, *Pharm. Zentralh.* **107**, 444 (1968); *Chem. Abstr.* **69**, 106601 (1968).

¹⁸¹ N. P. Buu-Hoi, G. Saint-Ruf, J. C. Perche, and J. C. Bourgeade, *Chim. Ther.* **3**, 110 (1968).

¹⁸² Ciba, Ltd., Netherlands Patent 6,507,422 (1965); *Chem. Abstr.* **65**, 2227 (1966).

¹⁸³ R. C. Elderfield and J. R. Wood, *J. Org. Chem.* **27**, 2463 (1962).

¹⁸⁴ H. Hellmann and I. Loschmann, *Chem. Ber.* **87**, 1684 (1954).

¹⁸⁵ B. Lucka-Sobstel and A. Zeje, *Diss. Pharm. Pharmacol.* **24**, 585 (1972).

¹⁸⁶ A. Lwoff, M. Sy, M. Maillet, J. Pages, and P. David, German Patent 2,023,551 (1970); *Chem. Abstr.* **74**, 53515 (1971).

¹⁸⁷ G. R. Pettit and J. A. Settepani, *J. Org. Chem.* **27**, 1714 (1962).

¹⁸⁸ H. J. Roth, *Arch. Pharm.* **294**, 623 (1961).

¹⁸⁹ H. J. Roth and H. H. Lausen, *Arch. Pharm.* **306**, 767 (1973).

¹⁹⁰ R. S. Varma and W. L. Nobles, *J. Heterocycl. Chem.* **3**, 462 (1966).

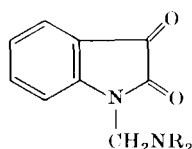
¹⁹¹ R. S. Varma and W. L. Nobles, *J. Med. Chem.* **10**, 510 (1967).

¹⁹² R. S. Varma and W. L. Nobles, *J. Med. Chem.* **10**, 972 (1967).

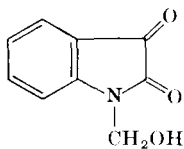
¹⁹³ John Wyeth and Brother Ltd., British Patent 1,240,648 (1971); *Chem. Abstr.* **75**, 118342 (1971).

^{193a} G. Saint-Ruf and J. C. Bourgeade, *Chim. Ther.*, 447 (1973).

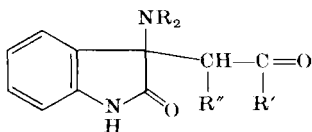
aldehyde gave **43**. Compounds such as $\text{Me}_2\text{NCH}_2\text{NHCOPh}$,¹⁹⁴ and $\text{Et}_2\text{NCH}_2\text{CHPhOH}$ ¹⁸⁸ (the latter by lead tetraacetate cleavage to the iminium salt) also react to give Mannich-type products (**42**). Michler's



(42)



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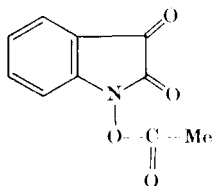


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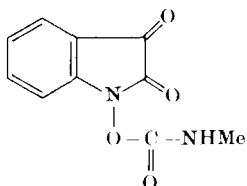
hydrol ($p\text{-Me}_2\text{NC}_6\text{H}_4$)₂CHOH,¹⁹⁵ gives an analogous condensation product [**41**, $\text{R} = \text{CH}(\text{C}_6\text{H}_4\text{NMe}_2)_2$]. Although isatin is generally aminomethylated at the NH-position, it also has been used as the electrophilic component in the Mannich reaction.¹⁸⁹ Thus isatin with $\text{R}'\text{COCH}_2\text{R}''$ and R_2NH gave **44**.

B. REACTIONS OF N-SUBSTITUENTS

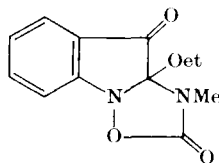
N-Substituted isatins have also been prepared by reactions of some of the compounds that were described earlier. Reaction of N-hydroxyisatin with acetic anhydride gave **45**.¹⁹⁶ N-Hydroxyisatin has been converted into **45a** by reaction with methyl isocyanate in the presence



(45)

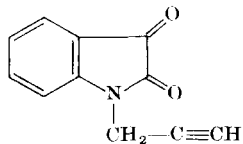


(45a)

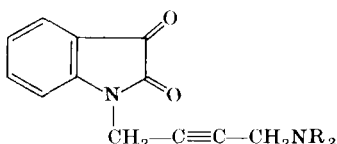


(45b)

of a catalytic amount of phenyldiazomethane.^{196a} Reaction of **45a** with catalytic phenyldiazomethane in ethanol gave the oxadiazolo[2,3-*a*]-indole **45b**.^{196a} Hydrolysis of **38** gave the corresponding propionic acid derivative.^{169,170} N-Propargylisatin (**46**) has been used in the Mannich



(46)



(47)

¹⁹⁴ H. Hellmann and G. Haas, *Chem. Ber.* **90**, 50 (1957).

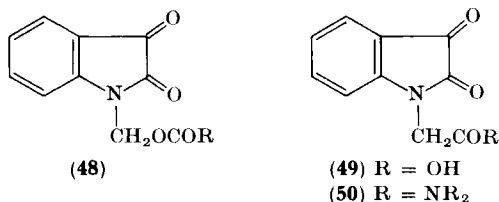
¹⁹⁵ H. Hellmann and G. Opitz, *Justus Liebigs Ann. Chem.*, **604**, 214 (1957).

¹⁹⁶ B. Eistert, G. Borggreffe, and H. Selzer, *Justus Liebigs Ann. Chem.* **725**, 37 (1969).

^{196a} L. Capuano and M. Zander, *Chem. Ber.* **100**, 3520 (1967).

reaction to give **47**.¹⁵⁹ Isatin Mannich reaction products have been reacted with active hydrogen compounds.¹⁹⁷ Thus, for example, **42** and acetophenone gave isatin and $\text{PhCOCH}_2\text{CH}_2\text{NR}_2$.¹⁹⁷

The hydroxymethyl compound **43** with acyl halides gave esters of the type **48**.¹⁶⁶ The acid **49** has reacted via the acyl chloride to give a number of amides of the type **50**.^{154,156} Thionyl chloride converts **43**



into chloromethylisatin.¹⁹⁸ Chloromethylisatin has proved to be a valuable reagent for the synthesis of N-substituted isatins. Reaction of chloromethylisatin with a large selection of compounds has led to a great variety of 1-isatinylmethyl derivatives.^{198-203a}

IV. Electrophilic Substitution and Related Reactions

A. HALOGENATION

Reagents such as *N*-bromosuccinimide,²⁰⁴ *N*-chlorosuccinimide,²⁰⁴ *N*-bromocaprolactam,²⁰⁵ sulfuryl chloride,²⁰⁶ bromine,¹¹⁸ and *t*-butylhypochlorite⁴⁸ have been used to prepare 5-haloisatins. Isatin with ICl gives 5-iodoisatin.²⁰⁷ Chlorination of 6-chloroisatin^{40,208} and 4-chloroisatin⁴⁰ gave 5,6- and 4,5-dichloroisatin, respectively. Various alkylisatins also undergo halogenation in the 5-position.^{11,21}

¹⁹⁷ W. L. Nobles and N. D. Potti, *J. Pharm. Sci.* **57**, 1097 (1968).

¹⁹⁸ F. Knotz, *Sci. Pharm.* **38**, 227 (1970).

¹⁹⁹ H. Boehme and H. H. Otto, *Arch. Pharm. (Weinheim)* **300**, 922 (1967).

²⁰⁰ H. Boehme and H. Schwartz, *Arch. Pharm. (Weinheim)* **306**, 684 (1973).

²⁰¹ F. Knotz, *Sci. Pharm.* **38**, 26 (1970).

²⁰² F. Knotz, *Sci. Pharm.* **41**, 123 (1973).

²⁰³ W. Wendelin and F. Knotz, *Monatsh. Chem.* **103**, 1632 (1972).

^{203a} K. Issleib, W. D. Hepp, H. Oehme, and G. Erfurt, East German Patent 98,935 (1973); *Chem. Abstr.* **80**, 70697 (1974).

²⁰⁴ N. P. Buu-Hoi, *Rec. Trav. Chim.* **73**, 197 (1954).

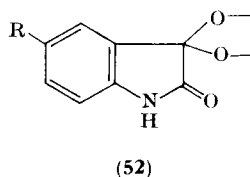
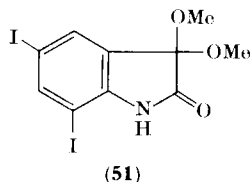
²⁰⁵ B. Taub and J. B. Hino, *J. Org. Chem.* **25**, 263 (1960).

²⁰⁶ H. Junnge and H. J. Quadbeck-Seeger, German Patent 2,158,955 (1973); *Chem. Abstr.* **79**, 66169 (1973).

²⁰⁷ N. P. Buu-Hoi and P. Jacquignon, *C.R. Acad. Sci.* **244**, 786 (1957).

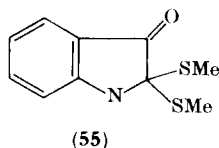
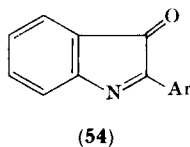
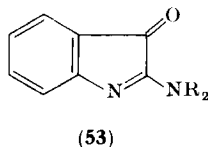
²⁰⁸ M. M. Rapport, A. E. Senear, J. F. Mead, and J. B. Koepfli, *J. Amer. Chem. Soc.* **68**, 2697 (1946).

If the 5-position is occupied, halogenation takes place in the 7-position. Bromination of 5-chloro or 5-methylisatin leads to the corresponding 7-bromo compounds,^{21,209} and reaction of 4-chloro-5-methoxyisatin with *N,N*-dichlorourethane in refluxing acetic acid gave 4,7-dichloro-5-methoxyisatin.¹³⁶ In aqueous acetic acid these latter reactants gave 1,4-dichloro-5-methoxyisatin.¹³⁶ Attempts to introduce a second iodine in 5-iodoisatin led to the isolation of **51**, which could be



hydrolyzed to 5,7-diiodoisatin.²¹⁰ Reaction of a number of 5-substituted ketals (**52**) with ICl led to the isolation of 7-iodo-5-substituted ketals, which could be hydrolyzed to the 7-iodo-5-substituted isatins.²¹⁰

Although not electrophilic substitution, halogens have also been introduced into the 2- and 3-positions. Reagents such as phosphorus pentachloride^{32,211-213,216} and chlorosulfonic acid²¹⁴ have been used to introduce a halogen into the 2-position of isatins giving 2-chloro-3-oxoindolenines. The products react further with reagents such as secondary amines,²¹¹ reactive aromatic compounds,^{211,213,215} and thiols²¹² to give compounds such as **53**, **54**, and **55** respectively.



²⁰⁹ R. F. Coles, U.S. Patent 2,642,439 (1953); *Chem. Abstr.* **48**, 4004 (1954).

²¹⁰ R. J. Bass, *Tetrahedron Lett.*, 1087 (1971).

²¹¹ J. vanAlphen, *Rec. Trav. Chim.* **60**, 138 (1941).

²¹² J. T. Baker and C. C. Duke, *Tetrahedron Lett.*, 43 (1968).

²¹³ E. Sawicki, T. W. Stanley, T. R. Hauser, and R. Barry, *Anal. Chem.* **31**, 1664 (1959).

²¹⁴ W. Langenbeck and D. Heuchel, *Monatsh. Chem.* **98**, 535 (1967).

²¹⁵ E. Sawicki, T. W. Stanley and W. Elbert, *Microchem. J., Symp. Ser.* **2**, 633 (1961).

²¹⁶ G. Palazzo and V. Rosnati, *Gazz. Chim. Ital.* **83**, 211 (1953).

B. OTHER ELECTROPHILIC SUBSTITUTIONS

Nitration of isatin,^{217,218} 7-methylisatin,⁸ 4,7-dimethylisatin,²¹ and 1-ethylisatin¹⁴⁷ leads to the introduction of the nitro group into the 5-position. Nitration of 5-methylisatin gave 5-methyl-7-nitroisatin.^{8,21}

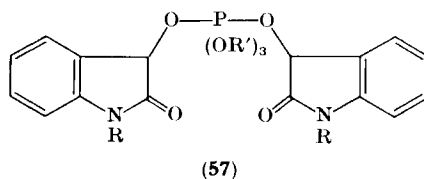
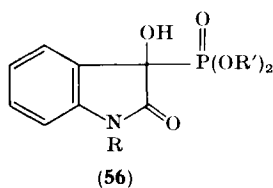
Reaction of isatin and haloisatins with chlorosulfonic acid gave 5-chlorosulfonylisatins²¹⁹ which were then converted into sulfonamides.

C. OTHER TRANSFORMATIONS

A number of reactions that do not reasonably fit in other categories are included in this section.

The methoxy group in 7-methoxy,² 7-methoxy-6-methyl,⁴¹ and 7-methoxy-4-methylisatin⁴¹ has been cleaved to the corresponding hydroxy group with pyridine hydrochloride, while treatment with sodium hydroxide cleaves the 6-methoxy group of 5-chloro-6,7-dimethoxy-1-methylisatin.⁴⁸ 5-Acetamidoisatins have been hydrolyzed to 5-aminoisatins.³⁰ Isatin carboxylic acids have been converted to amides and esters by means of standard procedures.^{52,53}

A number of complexes of isatin and metal salts have been reported.^{220,221} Isatin and N-substituted isatins react with dialkyl phosphites to give **56** and with trialkyl phosphites to give **57**.²²² The pyrolysis products of isatin have been studied,²²³ as have those of N-methylisatins.^{223a}



²¹⁷ W. C. Sumpter and W. F. Jones, *J. Amer. Chem. Soc.* **65**, 1802 (1943)

²¹⁸ M. J. Taglianetti, *An. Fac. Farm. Odontol., Univ. Sao Paulo* **7**, 57 (1949); *Chem. Abstr.* **45**, 1997 (1951).

²¹⁹ S. Somasekhara, V. S. Dighe, G. K. Suthar, and S. L. Mukherjee, *Curr. Sci.* **34**, 508 (1965).

²²⁰ R. C. Paul and S. L. Chadha, *J. Inorg. Nucl. Chem.* **31**, 2753 (1969).

²²¹ R. C. Paul, S. K. Rehani, and S. L. Chadha, *Indian J. Chem.* **8**, 848 (1970).

²²² A. Mustafa, M. M. Sidky, and F. M. Soliman, *Tetrahedron* **22**, 393 (1966).

²²³ W. D. Crow and C. Wentrup, *Chem. Commun.*, 1026 (1968).

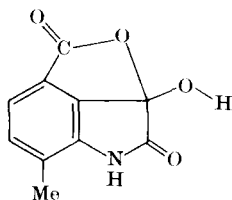
^{223a} C. Wentrup, *Helv. Chim. Acta* **55**, 1613 (1972).

V. Spectral Properties

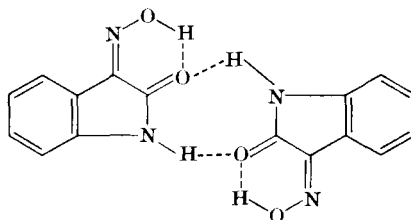
A. INFRARED

Extensive studies have been reported on infrared vibrational frequency correlations of isatin and a variety of substituted isatin.^{79,167,224-228} Infrared evidence supports structure **1** for isatin and gives no evidence for the lactim or enol form.^{225,229} In contrast to isatin infrared studies indicate that the so-called 4,5,6,7-tetrahydroisatins exist as the enol tautomer **19**.⁷⁹

In concentrated solution 7-methylisatin-4-carboxylic acid exhibits normal carboxylic acid dimerization, but in the solid state the lactol form **58** is present.²²⁸ Infrared studies indicate that hydrogen bonding as shown in **59** best represents the structure and mode of association of



(58)



(59)

isatin-3-oximes.²²⁷ The infrared and hydrogen bonding of isatin-3-thiosemicarbazones have been studied.²³⁰ An infrared study of the interaction of dimethylsulfoxide and isatin has appeared.²³¹

B. OTHER SPECTRAL STUDIES

A number of studies of the ultraviolet absorption spectra of isatins have appeared.^{34,232-235} The absorption curves of isatin and *N*-methylisatin are practically identical.²³³

²²⁴ D. G. O'Sullivan, *J. Chem. Soc.*, 3278 (1960).

²²⁵ D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2202 (1956).

²²⁶ D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2839 (1957).

²²⁷ D. G. O'Sullivan and P. W. Sadler, *J. Org. Chem.* **22**, 283 (1957).

²²⁸ P. W. Sadler, H. Mix, and H. W. Krause, *J. Chem. Soc.*, 667 (1959).

²²⁹ K. Kurosaki, *Nippon Kagaku Zasshi* **82**, 1555 (1961); *Chem. Abstr.* **58**, 12088 (1963).

²³⁰ P. W. Sadler, *J. Chem. Soc.*, 957 (1961).

²³¹ R. C. Paul, P. Singh, and S. L. Chadha, *Indian J. Chem.* **6**, 673 (1968).

²³² S. J. Angyal, E. Bullock, W. G. Hanger, W. C. Howell, and A. W. Johnson, *J. Chem. Soc.*, 1592 (1957).

²³³ A. Mangini and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna* **9**, 51 (1951); *Chem. Abstr.* **46**, 350 (1952).

Isatin has been reported to fragment predominantly by successive loss of CO, HCN, and CO from the molecular ion on electron impact, and also by consecutive loss of two molecules of CO from the molecular ion followed by loss of HCN.²³⁶ Use of 3-¹³C-labeled isatin shows that the initial loss of CO occurs entirely from the 2-position.²³⁷ Mass spectral studies have also been carried out on a variety of derivatives of isatin.²³⁶⁻²⁴¹

NMR studies have confirmed the enol tautomer **19** for the so-called tetrahydroisatins,⁸¹ and support the hydrazone structure for *N*-methylisatin-3-phenylhydrazone.²⁴²

VI. Oxidation and Reduction

A. OXIDATION

The most frequently reported oxidation reaction of isatins is the oxidation with alkaline hydrogen peroxide to give anthranilic acids. This procedure has been both as a proof of structure of isatins and as a method of synthesis of anthranilic acids. The oxidation has been applied to alkyl,^{8,10,11,23,33,38-40,46,49,50,118} halo,^{11,18,35,36,38-40,47,106,118,119,136,240} alkoxy,^{25,38,39,47,75,107,118,136} trifluoromethyl,^{33,38,137} and nitro^{8,120,217} isatins. Use of *N*-substituted isatins led to *N*-substituted anthranilic acids.^{66,71,125,158,169,243} In the oxidation of 5-bromo-1-(γ -carbethoxypropyl)-7-ethylisatin, **60** was isolated after treatment with ethanol and acid.¹¹ Oxidation of isatin derivatives **61** led, after treatment with diazomethane, to the acridine derivatives **62**.⁶⁷ Application of this oxidation method to 7-hydroxyisatins gave rise to benzoxazolones (**63**).^{2,41}

²³⁴ A. Mangini and R. Passerini, *Boll. Sci. Fac. Chim. Ind. Bologna* **12**, 150 (1954); *Chem. Abstr.* **49**, 8701 (1955).

²³⁵ R. Pummerer, F. Meininger, G. Schrott, and H. Wagner, *Justus Liebigs Ann. Chem.* **590**, 195 (1954).

²³⁶ J. A. Ballantine, R. G. Fenwick, and M. Alam, *Org. Mass. Spectrom.* **1**, 467 (1968).

²³⁷ M. Butcher, *Org. Mass Spectrom.* **5**, 759 (1971).

²³⁸ J. A. Ballantine, R. G. Fenwick, and F. D. Popp, *Org. Mass Spectrom.* **5**, 1003 (1971).

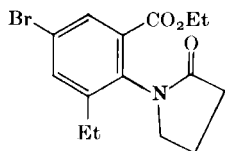
²³⁹ F. D. Popp, *J. Heterocycl. Chem.* **6**, 125 (1969).

²⁴⁰ F. D. Popp, *J. Heterocycl. Chem.* **9**, 1399 (1972).

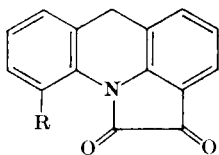
²⁴¹ K. Yamada, T. Konakahara, and H. Iida, *Kogyo Kagaku Zasshi* **73**, 980 (1970).

²⁴² F. A. Snively and C. H. Yoder, *J. Org. Chem.* **33**, 513 (1968).

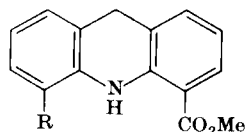
²⁴³ C. Clerc-Bory, M. Clerc-Bory, H. Pacheco, and C. Mentzer, *Bull. Soc. Chim. Fr.* **1229** (1955).



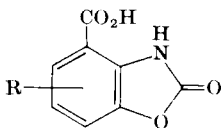
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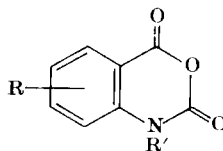
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(62)



(63)

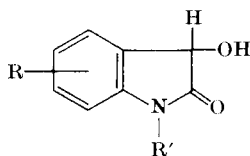


(64)

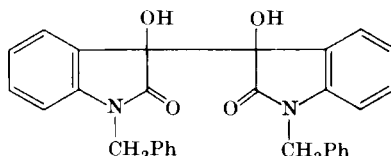
Oxidation with chromium trioxide in acetic acid,³³ chromium trioxide in acetic anhydride-acetic acid,³¹ 3-chloroperbenzoic acid in methylene chloride⁶⁵ or benzene,⁷⁴ or peracetic acid in acetic acid⁷⁴ gave rise to isatoic anhydrides (64).

B. REDUCTION

Sodium hydrosulfite has been used to reduce 5-bromo and 5,7-dibromoisatin²⁴⁴ as well as 5-methoxy-1-methylisatin⁵⁷ to the corresponding dioxindole (65). Reduction of 1-benzylisatin with sodium hydrosulfite led to the dioxindole (65, R = H, R' = CH₂Ph)^{111,245} and the isatide (66).²⁴⁵ 1,7-Trimethyleneisatin¹¹⁰ underwent a similar



(65)



(66)

reduction. 66 was also obtained from 65 and 1-benzylisatin.²⁴⁵ Sodium borohydride also converted 1-benzylisatin to the dioxindole.¹⁵⁰

Reduction of 5-chloroisatin with a zinc-copper couple led to 5-chlorooxindole.^{137a} A sodium-butanol reduction of 4,6-dimethoxyisatin led to the corresponding indole.⁹⁴

Lithium aluminum hydride reduction of isatin gave mixtures of 3-hydroxyindoline, indole, indigo, and indirubin with compositions depending upon the experimental conditions.²⁴⁶ The latter three products

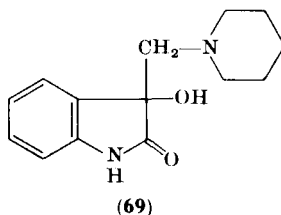
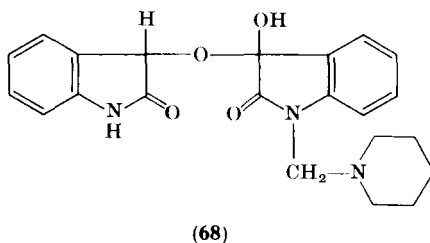
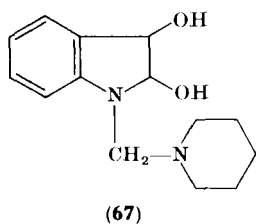
²⁴⁴ W. C. Sumpter, *J. Amer. Chem. Soc.* **67**, 1140 (1945).

²⁴⁵ G. Hallmann, *Chem. Ber.* **95**, 1138 (1962).

²⁴⁶ E. Giovannini and T. Lorenz, *Helv. Chim. Acta* **40**, 1553 (1957).

were also obtained from a similar reduction of the 2- and 3-oximes of isatin.²⁴⁷ Lithium aluminum hydride reduction of *N*-methylisatin gave *N*-methylindole and *N,N'*-dimethylindigo while *N*-methylisatin-3-oxime gave *N*-methylindole and *N,N'*-dimethylindirubin.²⁴⁸ In a similar manner 5-methylisatin gave 5,5'-dimethylindirubin.^{249,250}

Generally, however, lithium aluminium hydride reduction is used to convert isatins to indoles. Thus, 4,5,6-trimethoxyisatin,²⁵¹ 5-bromoisatin,²⁵² 5-chloro-6-methoxy-1-methylisatin,²⁵³ 1-ethyl- and 1-methylisatin,²⁵⁴ and 4,6-dimethoxyisatin⁹⁴ all gave the corresponding indoles.



1-Piperidinomethylisatin on lithium aluminum hydride gave the indoline **67** while sodium borohydride reduction of the same isatin derivative gave a reductive dimerization to **68** and a reduction-rearrangement to **69**.²⁵⁵

Catalytic hydrogenation of isatin and *N*-methylisatin gave oxindole and *N*-methyloxindole,²⁵⁶ while similar reduction of 1-azidoacetylisatin gave 1-aminoacetyloxindole.¹⁶⁵ Catalytic hydrogenation over platinum oxide of *N*-methylisatin and isatin-1-propionic acid gave **70**.¹⁶⁹ A

²⁴⁷ E. Giovannini and T. Lorenz, *Helv. Chim. Acta* **40**, 2287 (1958).

²⁴⁸ E. Giovannini and T. Lorenz, *Helv. Chim. Acta* **41**, 113 (1958).

²⁴⁹ T. Ozawa and N. Kinae, *Chem. Pharm. Bull.* **18**, 1293 (1970).

²⁵⁰ T. Ozawa and N. Kinae, *Yakugaku Zasshi* **93**, 8 (1973).

²⁵¹ A. Carlsson, H. Corrodi, and T. Magnusson, *Helv. Chim. Acta* **46**, 1231 (1963).

²⁵² M. Julia, Y. Huang, and J. Igolen, *C.R. Acad. Sci., Ser. C* **265**, 110 (1967).

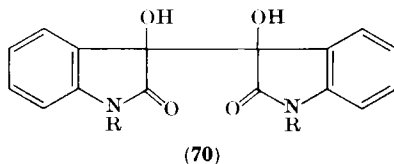
²⁵³ H. Reimann and R. Jaret, *Chem. Ind., (London)* 2173 (1967).

²⁵⁴ C. B. Hudson and A. V. Robertson, *Aust. J. Chem.* **20**, 1699 (1967).

²⁵⁵ H. J. Roth and H. H. Lausen, *Arch. Pharm. (Weinheim)* **306**, 775 (1973).

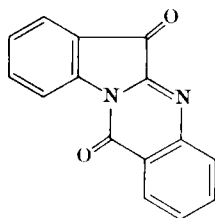
²⁵⁶ J. M. Muchowski, *Can. J. Chem.* **47**, 857 (1969).

variety of substituted indoles have been obtained by diborane reduction of isatins.²⁵⁷



Isatin, *N*-methylisatin, and *N*-hydroxyisatin can be reduced to semidiones by treatment with the enolate anion of propiophenone in dimethylsulfoxide.²⁵⁸ Nitroxides are prepared from *N*-hydroxyisatin by treatment with lead dioxide in dioxan, while another nitroxide was formed spontaneously from *N*-hydroxyisatin in basic dimethyl sulfoxide solution in the presence of oxygen.²⁵⁸

Stannous chloride reduction, in an acidic ethanol solution, of 1-(*o*-nitrobenzoyl)isatin followed by treatment with base gave **71**.¹⁵³



Electrolytic reduction of isatin²⁵⁹ using a lead electrode and a saturated sodium carbonate solution as electrolyte gave dihydroxy-indole, whereas a mercury cathode and lead anode in neutral sodium sulfate gave hydroxyindole. Electrolytic reduction of 1-methylisatin²⁶⁰ using lead cathodes and 20% sulfuric acid gave 1-methyldihydroxy-indole; a mercury cathode and neutral sodium sulfate gave 1-methyl-hydroxyindole.

The polarographic behaviour of isatin,²⁶¹⁻²⁶⁵ *N*-alkylisatin,²⁶⁵

²⁵⁷ H. Sirowej, S. A. Khan, and H. Plieninger, *Synthesis*, **84** (1972).

²⁵⁸ G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer, and R. Blankespoor, *J. Amer. Chem. Soc.* **92**, 2762 (1970).

²⁵⁹ B. Sakurai, *Bull. Chem. Soc. Jap.* **17**, 269 (1942).

²⁶⁰ B. Sakurai, *J. Shinshu Univ.* **1**, 1 (1951); *Chem. Abstr.* **48**, 12580 (1954).

²⁶¹ H. Cassebaum, *Z. Elektrochem.* **58**, 515 (1954).

²⁶² W. Kemula, M. K. Kalinowski, and A. Girdwoyn, *Rocz. Chem.* **41**, 1975 (1967).

²⁶³ I. A. Korshunov, L. N. Sazanova, M. K. Shehennikova, and O. P. Malkova, *Zavod. Lab.* **15**, 1287 (1949); *Chem. Abstr.* **44**, 3845 (1950).

²⁶⁴ W. C. Sumpter, J. L. Williams, P. H. Wilkens, and B. L. Willoughby, *J. Org. Chem.* **14**, 713 (1949).

²⁶⁵ W. C. Sumpter, P. H. Wilken, J. L. Williams, R. Wedemeyer, S. L. Boyer, and W. W. Hunt, *J. Org. Chem.* **16**, 1777 (1951).

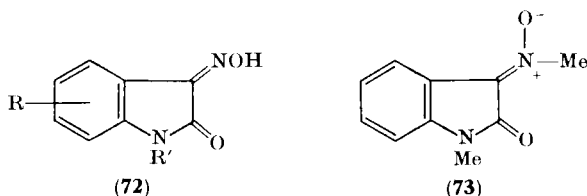
isatin-3-oxime,^{266,267} isatin-3-hydrazone,²⁶⁸ 3-phenyliminooxindoles,²⁶⁹ 3-benzylideneindol-2(3*H*)-ones,²⁷⁰ 1-(chloroacetyl)isatin,²⁷¹ and a variety of isatin derivatives²⁶¹ has been studied. A polarographic study of the alkaline hydrolysis of an isatin anil has been carried out.²⁷²

An analytical procedure for organotin hydrides has been based on the reduction of isatin to oxindole.²⁷³

VII. Reactions with Ketone Reagents

A. OXIMES

A wide variety of substituted isatins have reacted with hydroxylamine to give isatin-3-oximes (**72**).^{6,26,42,51,92,107,126,169,274} O-Substituted hydroxylamines also give this reaction.²⁷⁵ 5-Bromoisatin-3-oxime



has been prepared by reaction of 5-bromooxindole with sodium nitrite in acetic acid²⁷⁶ and further examples of this reaction are included in Section II,C. *N*-Methylisatin with *O*-methylhydroxylamine gives 1-methylisatin-3-*O*-methyloxime, while *N*-methylisatin and *N*-methylhydroxylamine give **73**.²⁷⁷ Compound **73** can also be obtained from isatin-3-oxime with dimethyl sulfate and alkali.²⁷⁷

²⁶⁶ R. Andruzzi, M. E. Cardinali, I. Carelli, and A. Trazza, *Ann. Chim. (Rome)* **61**, 415 (1971).

²⁶⁷ C. Calzolari, *Boll. Soc. Adriat. Sci., Nat. Trieste* **45**, 109 (1949); *Chem. Abstr.* **46**, 3423 (1952).

²⁶⁸ M. Cardinali, I. Carelli, and A. Trazza, *Ric. Sci.* **39**, 647 (1969).

²⁶⁹ A. Kosturiak and A. Nincakova, *Petrochemia* **13**, 30 (1973).

²⁷⁰ L. C. Chatten, R. W. Daisley, and C. J. Olliff, *J. Chem. Soc., Perkin Trans. 2*, 469 (1973).

²⁷¹ Y. V. Svetkin and L. N. Andreeva, *Zh. Obshchei Khim.* **36**, 8 (1966).

²⁷² A. Kosturiak and R. Domansky, *Chem. Zvest.* **27**, 227 (1973).

²⁷³ M. Frankel, D. Wagner, D. Gertner, and A. Zilkla, *Isr. J. Chem.* **4**, 183 (1966).

²⁷⁴ G. R. Bedford and M. W. Partridge, *J. Chem. Soc.*, 1633 (1959).

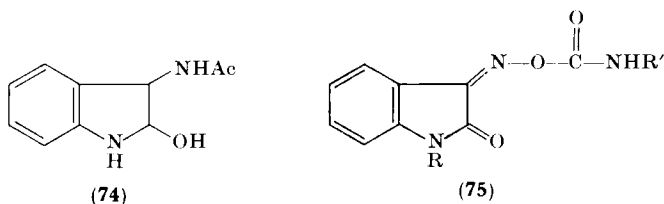
²⁷⁵ F. J. Villani, R. F. Tavares, and C. A. Ellis, *J. Pharm. Sci.* **58**, 138 (1969).

²⁷⁶ W. C. Sumpter, M. Miller, and L. N. Hendrick, *J. Amer. Chem. Soc.* **67**, 1656 (1945).

²⁷⁷ B. Eistert, R. Muller, H. Selzer, and E. A. Hackmann, *Chem. Ber.* **97**, 2469 (1964).

Isatin-3-oximes readily form complexes with a variety of metal ions.^{278,279} In a number of cases, these have seen analytical applications.^{6,42,280-283} Isatin-2-oximes¹ also form metal complexes.^{279,284-287}

Reduction of isatin-3-oximes to the corresponding 3-aminooxindole has been carried out using stannous chloride in acetic acid⁵¹ or in hydrochloric acid.⁹² 3-Aminooxindole has also been obtained by electrochemical reduction²⁸⁸ and catalytic hydrogenation.¹⁶⁹ Reduction



of isatin-3-oxime with zinc in acetic acid-acetic anhydride gave **74**, which was converted into 2-methylindolo[3,2-*d*]thiazole by phosphorus pentasulfide.^{289,289a}

Isatin-3-oxime reacts with isocyanates to give carbamoyloximino-isatins (**75**).²⁹⁰ Irradiation of *N*-methylisatin-3-oxime causes syn-anti isomerization,²⁹¹ while *N*-acetyloxindolone is obtained from irradiation of *N*-acetylisatindioxime.²⁹¹ Treatment of this dioxime with acetic

²⁷⁸ L. Divis, *Sb. Vys. Sk. Chem.-Technol. Praze, Anal. Chem.*, **3**, 85 (1968); *Chem. Abstr.* **73**, 10333 (1970).

²⁷⁹ K. Eckschlager, *Chem. Listy* **56**, 489 (1962).

²⁸⁰ F. Buscarons and A. Izquierdo, *Inform. Quim. Anal.* **18**, 103 (1964); *Chem. Abstr.* **62**, 4615 (1965).

²⁸¹ V. Hovorka, V. Sykora, and J. Vorisek, *Chim. Anal.* **29**, 268 (1947).

²⁸² A. Izquierdo and G. Rauret, *Inform. Quim. Anal.* **23**, 161 (1969); *Chem. Abstr.* **72**, 128318 (1970).

²⁸³ L. S. Malowan, *Ciencia* **19**, 119 (1959); *Chem. Abstr.* **54**, 7412 (1960).

²⁸⁴ L. Divis, *Sb. Vys. Sk. Chem.-Technol. Praze, Anal. Chem.*, **5**, 21 (1969); *Chem. Abstr.* **73**, 126626 (1970).

²⁸⁵ L. Divis and J. Skoda, *Chem. Listy* **48**, 539 (1954).

²⁸⁶ V. Hovorka and L. Divis, *Collect Czech. Chem. Commun.* **14**, 116 (1949).

²⁸⁷ V. Hovorka and L. Divis, *Collect Czech. Chem. Commun.* **14**, 473 (1949).

²⁸⁸ R. Andruzzi, M. E. Cardinali, and A. Trazza, *Electrochim. Acta* **17**, 1524 (1972).

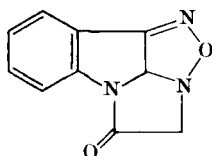
²⁸⁹ P. I. Abramenko, *Zh. Vses. Khim. Obshchest.* **16**, 231 (1971); *Chem. Abstr.* **75**, 5778 (1971).

^{289a} P. I. Abramenko, *Zh. Vses. Khim. Obshchest.* **18**, 714 (1973); *Chem. Abst.* **80**, 95808 (1974).

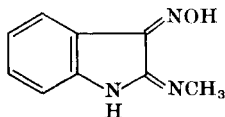
²⁹⁰ M. Giannella and M. Pignini, *Farmaco, Ed. Sci.* **28**, 157 (1973).

²⁹¹ T. Sasaki and M. Takahashi, *Yuki Gosei Kagaku Kyokai Shi* **26**, 899 (1968); *Chem. Abstr.* **70**, 28746 (1969).

anhydride causes cyclization to **76**, which on hydrolysis with potassium hydroxide yielded the isatin derivatives **77** and **78**.²⁹²



(76)

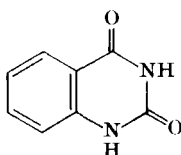


(77)

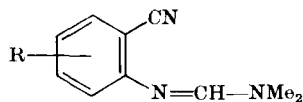


(78)

Treatment of a number of isatin-3-oximes with sodium methoxide at 140°²⁹³ or simply thermally^{274,294} leads to *o*-aminobenzonitriles. Thermal treatment of isatin-2-oxime gave isatin and **79**.²⁹⁴ Beckman rearrangement of isatin-3-oximes resulted in the formation of *o*-cyano-phenylisocyanates.^{26,295} With the Vilsmeier reagent, phosphorus



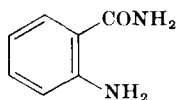
(79)



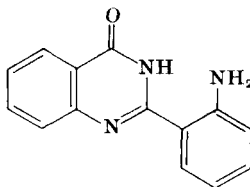
(80)

oxychloride-dimethylformamide, isatin-3-oximes gave *N,N*-dimethyl-*N'*-(*o*-cyanophenyl)formamidines (**80**).²⁹⁶ This reaction probably proceeds through the *o*-cyanophenylisocyanates.

The Schmidt reaction of isatin and hydrazoic acid in sulfuric acid gave anthranilamide (**81**), quinazoline-2,4-dione (**79**), and 2-(*o*-aminophenyl)-quinazolin-4-one (**82**).²⁹⁷ A similar reaction has been reported



(81)



(82)

²⁹² M. Takahashi, *Bull. Chem. Soc. Jap.* **43**, 2986 (1970).

²⁹³ Badische Anilin- und Soda-Fabrik A.-G., French Patent 2,014,431 (1970); *Chem. Abstr.* **74**, 22571 (1971).

²⁹⁴ G. Bargellini and C. J. Turi, *Gazz. Chim. Ital.* **84**, 157 (1954).

²⁹⁵ R. S. Pandit and S. Seshadri, *Indian J. Chem.* **11**, 532 (1973).

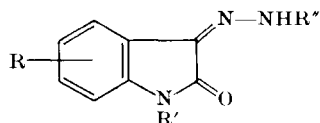
²⁹⁶ M. N. Deshpande and S. Seshadri, *Indian J. Chem.* **11**, 538 (1973).

²⁹⁷ G. Caronna and S. Palazzo, *Gazz. Chim. Ital.* **98**, 911 (1968).

to give simply anthranilamide from isatin^{294,298} and *N*-acetyl isatin,²⁹⁸ while *N*-ethyl isatin gave *o*-ethylaminobenzamide.²⁹⁸ 4-Chloro-, 6-chloro-, and 5-nitroanthranilamides were also prepared from the appropriate isatins although isatin-7-carboxylic acid failed to react.²⁹⁹

B. HYDRAZONES

A variety of arylhydrazines have been reacted with isatins to give isatin-3-arylhya zones (83).^{15,21,22,24,78,80,107,156,181,216,300-306} Similar reactions have also been carried out with isatins and alkylhydrazines,³⁰⁷ hydrazides,^{155,186,304,305,308-312} and hydrazine^{21,156,157,216,313-315} to give 84, 85, and 86, respectively. Aldehyde hydrazones also react with



(83) R' = Aromatic

(84) R' = Alkyl

(85) R' = Acyl

(86) R' = H

isatin.^{157,314} Isatin-3-phenylhydrazones were prepared from oxindoles and benzenediazonium chloride²⁷⁶ and from 3,3-dibromooxindoles and phenylhydrazine.^{137b,276} Isatin-3-(2-nitrophenylhydrazone) has exhibited antineoplastic activity in an animal screening system.³⁰⁵

Isatin-3-phenylhydrazones and various metal salts give rise to

²⁹⁸ G. Caronna, *Gazz. Chim. Ital.* **71**, 585 (1941).

²⁹⁹ W. G. H. Edwards and V. Petrow, *J. Chem. Soc.*, 1713 (1948).

³⁰⁰ E. Campaigne, R. L. Thompson, and J. E. VanWerth, *J. Med. Pharm. Chem.* **1**, 577 (1959).

³⁰¹ L. Capuano and W. Ebner, *Chem. Ber.* **104**, 2221 (1971).

³⁰² F. Feigl and D. Goldstein, *Talanta* **4**, 209 (1960).

³⁰³ M. Kamel and S. A. Amin, *U.A.R. J. Chem.* **9**, 139 (1966).

³⁰⁴ F. Knotz, *Sci. Pharm.* **38**, 222 (1970).

³⁰⁵ F. D. Popp, *J. Med. Chem.* **12**, 182 (1969).

³⁰⁶ H. Vanderhaegle and M. Claessen, *Bull. Soc. Chem. Belg.* **68**, 47 (1959).

³⁰⁷ R. H. Wiley and G. Irick, *J. Org. Chem.* **24**, 1925 (1959).

³⁰⁸ F. T. Bruderlein, U.S. Patent 3,558,646 (1971); *Chem. Abstr.* **75**, 5689 (1971).

³⁰⁹ N. P. Buu-Hoi, N. D. Xuong, N. H. Nam, F. Binon, and R. Royer, *J. Chem. Soc.*, 1358 (1953).

³¹⁰ V. S. Dimitrukha and P. S. Pelkis, *Khim. Geterotsikl. Soedin.* **7**, 1050 (1971).

³¹¹ A. Jensen and O. R. Hansen, *Acta Chem. Scand.* **6**, 195 (1952).

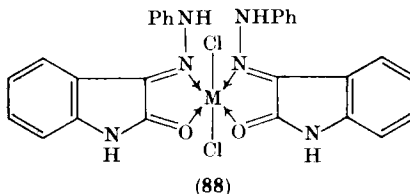
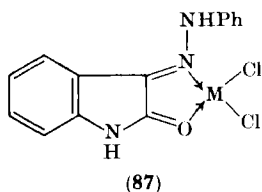
³¹² M. Sy, M. Maillet, and J. Pages, *Chim. Ther.* **5**, 216 (1970).

³¹³ M. Alam and J. A. Ballantine, *J. Chem. Soc. C*, 255 (1968).

³¹⁴ A. C. Padhya, H. J. Mehta, V. S. Dighe, and S. Somasekhara, *Sci. Cult.* **39**, 55 (1973).

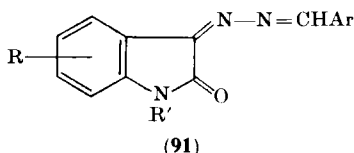
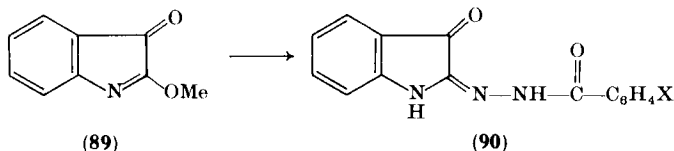
³¹⁵ T. Sasaki and M. Takahashi, *Yuki Gosei Kagaku Kyokai Shi* **26**, 901 (1968); *Chem. Abstr.* **70**, 37592 (1969).

complexes^{316,317} such as **87** ($M = \text{Cu, Zn, Cd}$) and **88** ($M = \text{Hg, Mn, Co}$). The complex formed from magnesium hydroxide and isatin-3-(4-nitrophenylhydrazine) has been used as a spot test for isatin.³⁰²



Reduction of **83** ($R = \text{H}$, $R' = \text{CH}_2\text{Ph}$, $R'' = \text{C}_6\text{H}_4\text{SO}_3\text{H}$) with Raney nickel alloy and sodium hydroxide gave 1-benzylidioxindole and with lithium aluminum hydride gave 1-benzylindoline.²¹⁶

Alkylation of **83** ($R' = \text{OH}$) takes a variety of paths including alkylation of the NOH to give 1-alkoxyisatins, alkylation of the NOH and the carbonyl group to give 1,2-dialkoxyindoles, alkylation at the hydrazone group, and ring expansion to 2-quinolones.³⁰¹ The course of the reaction depends upon the nature of the substituent in the side chain.



Reaction of **89** with hydrazides gave **90**.³¹⁰ The trans form was obtained and could be converted into the cis form thermally or photochemically and then reconverted by acid.³¹⁰

Isatin-3-hydrazones react with aldehydes to give **91**.^{157,314} Compound **91** ($R = \text{H}$, $\text{Ar} = 2\text{-(5-nitrofuryl)}$) has also been prepared by reaction of isatin with 5-nitrofurfuraldehyde hydrazone.³¹⁴ Ammonium isothiocyanate, and **86** gave isatin-3-thiosemicarbazones.³¹⁸

Heating of hydrazones **86** with sodium hydroxide gave oxindole and isatin azine,³¹⁹ and heating with sodium ethoxide gave oxindole,

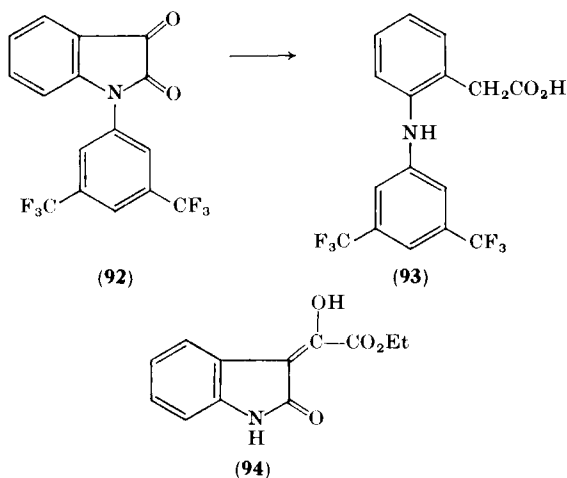
³¹⁶ M. N. Sharma, *Curr. Sci.* **42**, 92 (1973).

³¹⁷ F. I. M. Taha and M. A. Khatab, *U.A.R. J. Chem.* **13**, 227 (1970).

³¹⁸ V. P. Arya, Swiss. Patent 491,106 (1970); *Chem. Abstr.* **73**, 109673 (1970).

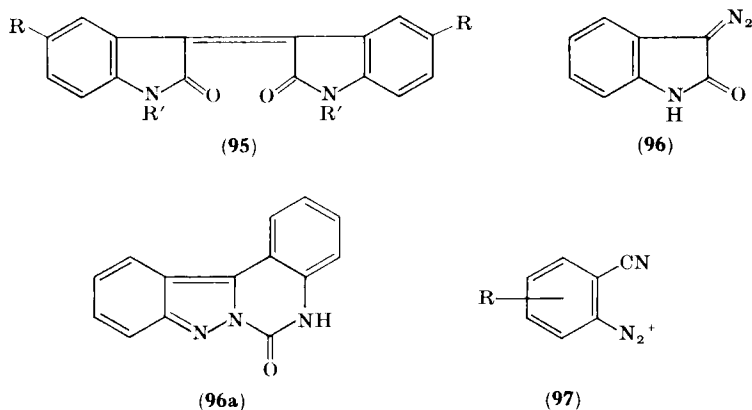
³¹⁹ W. Seibert, *Chem. Ber.* **80**, 494 (1947).

isoindigo, and 3,3'-bioxindolyl.³²⁰ The isoindigo probably arises from reaction of the oxindole and isatin while the bioxindolyl results from reduction of the isoindigo. Use of a stronger base, potassium *t*-butoxide in dimethyl sulfoxide, gave only isatin azine.³²⁰ The isatin **92** was



allowed to react with hydrazine and then warm sodium ethoxide to give **93**,⁷³ a product of both reduction and ring opening. Isatin-3-hydrazone was reduced with sodium in ethanol, and diethyl oxalate was added to give **94**.³¹³

Heating of isatin azines gave compounds of the type **95** ($R' = H$).³²¹ Treatment of 1-methylisatin-3-tosylhydrazone³²² with sodium in



³²⁰ A. H. Jackson, *Chem. Ind. (London)*, 1652 (1965).

³²¹ N. P. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 5035 (1968).

³²² E. J. Moriconi and J. J. Murray, *J. Org. Chem.* **29**, 3577 (1964).

ethylene glycol gave a similar product **95** ($R = H$, $R' = Me$).¹⁴⁴ Isatin-3-tosylhydrazone with sodium hydroxide gave 3-diazooxindole (**96**).^{322,323} Compound **96** was also prepared from **86** and mercuric oxide³²² and from isatin-3-oxime and chloramine.³²² 3-Diazooxindoles in methanol solution with a suitable Lewis acid provides a convenient source of 3-methoxyoxindoles.³²⁴ Pyrolysis and photolysis of **96** have also been studied.³²² Reaction of **96** with benzyne gave **96a**.^{324a} A similar reaction takes place between **96** and dimethyl acetylenedicarboxylate.^{324a}

Isatin-3-hydrazones (**86**) react with nitrosylsulfuric acid in glacial acetic acid to give, after dilution with water, the diazonium salt **97** as indicated by the formation of an azo dye with *N,N*-dimethylaniline.³²⁵

C. THIOSEMICARBAZONES AND RELATED COMPOUNDS

A very large variety of isatins reacted with thiosemicarbazides to give isatin-3-thiosemicarbazones (**98**).^{29,58,146,151,155,156,166,181,182,192,193a,200,304,312,315,326-344} The impetus for the bulk of this work is the fact

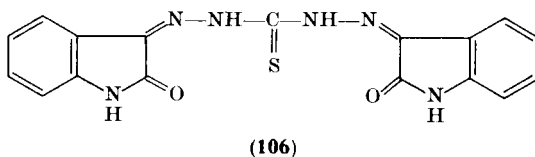
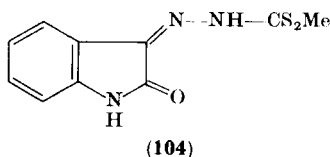
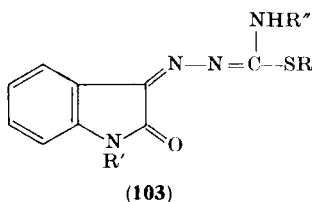
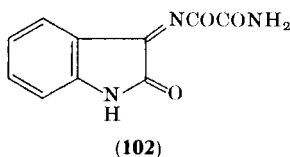
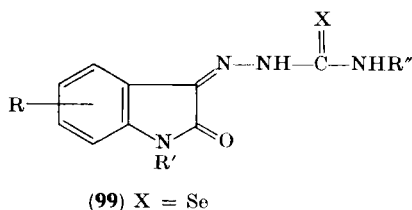
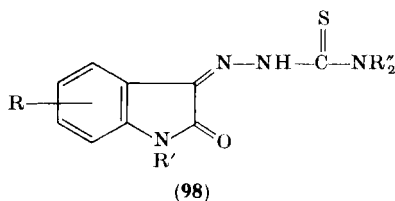
- ³²³ M. P. Cava, R. L. Little, and D. R. Napier, *J. Amer. Chem. Soc.* **80**, 2257 (1958).
³²⁴ P. L. Creger, *J. Org. Chem.* **30**, 3610 (1965).
^{324a} T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 1417 (1973).
³²⁵ T. Vaidyanathan and S. Seshadri, *Indian J. Chem.* **11**, 400 (1973).
³²⁶ D. J. Bauer and P. W. Sadler, *Nature (London)* **190**, 1167 (1961).
³²⁷ D. J. Bauer and P. W. Sadler, British Patent 975,357 (1964); *Chem. Abstr.* **62**, 6462 (1965).
³²⁸ D. J. Bauer and P. W. Sadler, U.S. Patent 3,253,991 (1966); *Chem. Abstr.* **65**, 8683 (1966).
³²⁹ J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins, and W. A. Lott, *J. Amer. Chem. Soc.* **73**, 906 (1951).
³³⁰ N. P. Buu-Hoi, N. D. Xuong, and F. Binon, *J. Chem. Soc.*, 713 (1956).
³³¹ E. Campaigne and W. L. Archer, *J. Amer. Chem. Soc.* **74**, 5801 (1952).
³³² J. Daunis, R. Jacquier, M. Rigail, and P. Viallefont, *Bull. Soc. Chim. Fr.* 2289 (1970).
³³³ G. Doleschall and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **64**, 369 (1970).
³³⁴ L. Heinisch and K. Kramarczyk, *J. Prakt. Chem.* **314**, 682 (1972).
³³⁵ Z. Holzbecher, *Chem. Listy* **44**, 126 (1950).
³³⁶ I. S. Ioffe, A. B. Tomehin, and E. N. Zhukova, *Zh. Obshch. Khim.* **39**, 70 (1969).
³³⁷ O. F. Lyman and N. M. Turkevich, *Meody. Poluch. Khim. Reaktivov Prep.*, 115 (1971); *Chem. Abstr.* **78**, 15950 (1973).
³³⁸ D. G. O'Sullivan, P. W. Sadler, and C. Webley, *Chemotherapy* **7**, 17 (1963).
³³⁹ B. Prescott, G. Jones, C. L. Peacock, and G. Caldes, *Antimicrob. Ag. Chemother.*, 275 (1969).
³⁴⁰ P. W. Sadler, *J. Chem. Soc.*, 243 (1961).
³⁴¹ S. Sallay and S. J. Childress, U.S. Patent 3,406,180 (1968); *Chem. Abstr.* **70**, 11223 (1969).
³⁴² A. W. Scott and M. A. McCall, *J. Amer. Chem. Soc.* **67**, 1767 (1945).

that several of these thiosemicarbazones exhibit significant antiviral activity.^{29,185,326,328,336,345-361b} It has also been claimed that *N*-ethylisatin-3-thiosemicarbazone has an effect on tonic convulsions.³⁶² Perhaps stimulated by the antiviral activity of isatin-3-thiosemicarbazone, isatin has been screened for a wide range of biological effects both in animals^{44,89,261,363-369} and in plants.³⁷⁰⁻³⁷⁵

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- ³⁴³ A. B. Tomchin, V. S. Dmitrukha, T. N. Timofeeva, and P. S. Pelkis, *Zh. Org. Khim.* **9**, 1988 (1973).
- ³⁴⁴ A. B. Tomchin, I. S. Ioffe, V. V. Tretyakova, Y. V. Lepp, and A. I. Koltsov, *Zh. Org. Khim.* **9**, 1537 (1973).
- ³⁴⁵ J. Aasen and G. Haukeness, *Acta Pathol. Microbiol. Scand., Sect. B* **80**, 246 (1972); *Chem. Abstr.* **77**, 57063 (1972).
- ³⁴⁶ M. Alexandrescu, L. Handruche, C. Murgescu, and M. Duca, *Rev. Roum. Inframicrobiol.* **6**, 219 (1969); *Chem. Abstr.* **73**, 11669 (1970).
- ³⁴⁷ M. Alexandrescu, C. Murgescu, L. Handrache, L. Ionescu, and M. Duca, *Stud. Cercet. Inframicrobiol.* **20**, 263 (1969).
- ³⁴⁸ D. J. Bauer, U.S. Patent 3,636,226 (1972); *Chem. Abstr.* **76**, 136008 (1972).
- ³⁴⁹ D. J. Bauer and G. Apostolov, *Science* **154**, 796 (1966).
- ³⁵⁰ D. J. Bauer, K. Apostolov, and J. W. T. Selway, *Ann. N.Y. Acad. Sci.* **173** (Art 1), 314 (1970); *Chem. Abstr.* **73**, 75217 (1970).
- ³⁵¹ R. Gabriel, *Brit. J. Exp. Pathol.* **52**, 271 (1971).
- ³⁵² R. F. Haff, J. J. Boyle, R. C. Stewart, R. J. Ferlauto, J. M. Z. Gladych, J. H. Hunt, and D. Jack, *Nature (London)* **221**, 286 (1969).
- ³⁵³ D. H. Jones, R. Slack, S. Squires, and K. R. H. Wooldridge, *J. Med. Chem.* **8**, 676 (1965).
- ³⁵⁴ W. Levinson, B. Woodson, and J. Jackson, *Nature (London)* **232**, 116 (1971).
- ³⁵⁵ L. G. Linitzkaya, G. A. Galegor, and R. M. Bikbulator, *Vop. Virusol.* **16**, 155 (1971); *Chem. Abstr.* **75**, 47125 (1971).
- ³⁵⁶ W. E. Magee and M. K. Back, *Ann. N.Y. Acad. Sci.* **130**, 80 (1965).
- ³⁵⁷ G. D. Pearson and E. F. Zimmerman, *Virology* **38**, 641 (1969).
- ³⁵⁸ G. D. Pearson and E. F. Zimmerman, *Biochim. Biophys. Acta* **195**, 246 (1969).
- ³⁵⁹ R. Pollikoff, M. Lieberman, N. E. Lem, and E. J. Foley, *J. Immunol.* **94**, 794 (1965); *Chem. Abstr.* **63**, 3505 (1965).
- ³⁶⁰ P. W. Sadler, *Ann. N.Y. Acad. Sci.*, **130**, 71 (1965).
- ³⁶¹ B. Woodson and W. K. Joklik, *Proc. Nat. Acad. Sci. U.S.* **54**, 946 (1965).
- ^{361a} E. Katz, E. Margalith, and B. Winer, *J. Gen. Virol.* **21**, 477 (1973).
- ^{361b} M. Tonew, E. Tonew, and L. Heinisch, *Acta Virol. (Engl. Ed.)* **18**, 17 (1974).
- ³⁶² M. Lieberman, R. Pollikoff, and A. M. Pascale, *Antimicrob. Ag. Chemother.*, 531 (1966).
- ³⁶³ F. Bruns, *Naturwissenschaften* **41**, 360 (1954).
- ³⁶⁴ J. Debat, German Patent 1,935,697 (1970); *Chem. Abstr.* **72**, 125053 (1970).
- ³⁶⁵ M. Mueller and S. Schultrich, *Acta Biol. Med. Ger.* **17**, 307 (1966); *Chem. Abstr.* **66**, 9718 (1967).
- ³⁶⁶ D. G. O'Sullivan and P. W. Sadler, *Arch. Biochem. Biophys.* **66**, 243 (1957).
- ³⁶⁷ K. Sareen, R. P. Kohli, M. K. P. Amma, and M. L. Gujral, *Indian J. Phys. Pharmacol.* **6**, 87 (1962).
- ³⁶⁸ T. J. Singh, *Indian Vet. J.* **48**, 672 (1971); *Chem. Abstr.* **76**, 81287 (1972).

Methods for the analysis of the antiviral *N*-methylisatin-3-thiosemicarbazone have been reported.³⁷⁶ Metabolic removal of the sulfur from *N*-methylisatin-3-thiosemicarbazone has been reported³⁷⁷ to give *syn*- and *anti*-*N*-methylisatin-3-semicarbazone.

A number of other analogs of **98**, such as **99**,³⁷⁸ **100**,^{332,335} **101**,^{379-380a} **102**,³⁸¹ **103**,^{333,334,336,382,383} **104**,³⁴⁰ and **105**,^{343,384} have been prepared.



³⁶⁹ I. Susheela, B. Singh, H. M. Dani, M. K. P. Amma, and K. Sareen, *Enzymologia* **37**, 325 (1969); *Chem. Abstr.* **72**, 74963 (1970).

³⁷⁰ H. R. Chen, A. W. Galston, and L. Milstone, *Plant. Physiol.* **41**, 1485 (1966).

³⁷¹ J. L. Foster, *Radiat. Prot. Sensitization. Proc. Int. Symp.*, 2nd, 299 (1969); *Chem. Abstr.* **74**, 20057 (1971).

³⁷² A. W. Galston and H. R. Chen, *Plant Physiol.* **40**, 699 (1965).

³⁷³ E. Hambsch, German Patent 1,013,459 (1957); *Chem. Abstr.* **54**, 16733 (1960).

³⁷⁴ S. Mukherji and T. Roy, *Indian J. Exp. Biol.* **10**, 395 (1972).

³⁷⁵ J. S. Weis, *Nature (London)* **211**, 1216 (1966).

³⁷⁶ J. C. Deavin and D. H. Mitchell, *J. Pharm. Pharmacol.* **17**, 565 (1965).

³⁷⁷ L. A. Nutting, E. M. Weber, and J. L. Tryon, *J. Virol.* **1**, 650 (1967).

³⁷⁸ J. Krajewski, *Rocz. Chem.* **46**, 1177 (1972).

An excess of isatin with thiocarbohydrazide gives **106**.³⁸⁴ The syn isomer of isatin-3-thiosemicarbazone predominates while isatin-3-semicarbazone exists in the anti form.³⁸⁵ Treatment with acid or warming converts this anti form into the syn isomer, while base causes the reverse isomerization.³⁴⁴ 4-Methylisatin-3-semicarbazone exists as the syn isomer.³⁴⁴

A variety of metal complexes of isatin-3-thiosemicarbazones^{279,386-390} and isatin-3-semicarbazones^{279,391} have been prepared.

A number of cyclization reactions have been carried out with isatin derivatives of this series. Isatin-3-thiosemicarbazone with chloroacetic acid, sodium acetate, acetic acid, and aldehydes gave **107**.^{392,393}

Treatment of isatin-3-thiosemicarbazone^{333,394,395} and N-methylisatin-3-thiosemicarbazone^{333,395} with 1N alkali gave **108** which on treatment with alkali and iodine gave **109**,³⁹⁵ and with alkali and methyl iodide gave **110**.^{333,396} Ring opening also took place in the preparation of **108** (R = Me).³³³ Treatment of **108** (R = Me) with

³⁷⁹ F. Baiocchi, C. C. Cheng, W. J. Haggerty, L. R. Lewis, T. K. Liao, W. H. Nyberg, D. E. O'Brien, and E. G. Podrebarac, *J. Med. Chem.* **6**, 431 (1963).

³⁸⁰ F. D. Popp, *J. Pharm. Sci.* **62**, 679 (1973).

^{380a} A. Lwoff, M. Sy, M. Maillet, J. Pages, and P. David, German Patent 2,020,230 (1970); *Chem. Abstr.* **74**, 22687 (1971).

³⁸¹ S. D. Moshchitskii, L. S. Sologub, A. F. Pavlenko, and V. P. Akkerman, *Zh. Org. Khim.* **2**, 2164 (1966).

³⁸² L. Heinisch, M. Tonew, and E. Tonew, German Patent 2,034,644 (1971); *Chem. Abstr.* **75**, 151669 (1971).

³⁸³ L. Heinisch, M. Tonew, and E. Tonew, British Patent 1,250, 598 (1971); *Chem. Abstr.* **76**, 3693 (1972).

³⁸⁴ A. B. Tomchin and I. S. Ioffe, *Zh. Org. Khim.* **8**, 199 (1972).

³⁸⁵ A. B. Tomchin, I. S. Ioffe, Y. V. Lepp, and A. I. Koltsov, *Zh. Org. Chem.* **9**, 1081 (1973).

³⁸⁶ P. Barz and H. F. Fritz, *Z. Naturforsch. B.* **25**, 199 (1970).

³⁸⁷ I. Grecu and M. Neamtu, *Rev. Chim. Miner.* **5**, 813 (1968); *Chem. Abstr.* **70**, 31995 (1969).

³⁸⁸ I. Grecu and M. Neamtu, *Rev. Chim. Miner.* **6**, 625 (1969); *Chem. Abstr.* **71**, 108568 (1969).

³⁸⁹ V. Hovorka and Z. Holzbecher, *Collect Czech. Chem. Commun.* **14**, 248 (1949).

³⁹⁰ G. N. Mitra and S. S. G. Sircar, *J. Indian Chem. Soc.* **32**, 435 (1955).

³⁹¹ V. Hovorka and Z. Holzbecher, *Collect Czech. Chem. Commun.* **14**, 186 (1949).

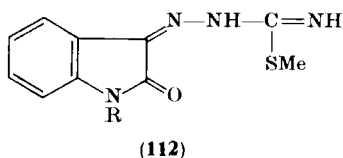
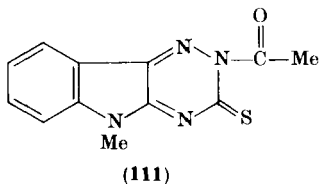
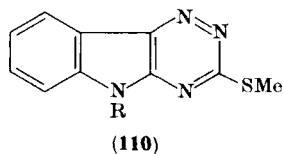
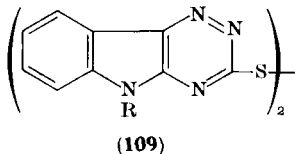
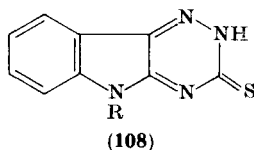
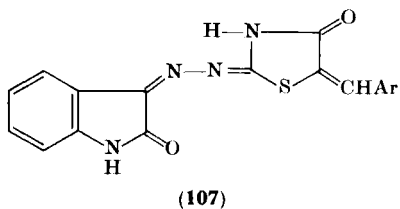
³⁹² I. M. Kazanovskaya, *Farm. Zh. (Kiev)* **27**, 59 (1972); *Chem. Abstr.* **77**, 61870 (1972).

³⁹³ N. M. Turkevich and O. F. Lyman, *Khim.-Farm. Zh.* **3**, 26 (1969); *Chem. Abstr.* **71**, 30314 (1969).

³⁹⁴ R. E. Hagenbach, E. Hodel, and H. Gysin, *Angew. Chem.* **66**, 359 (1964).

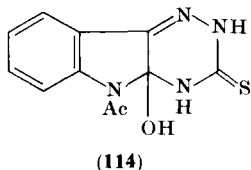
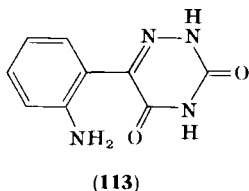
³⁹⁵ I. S. Ioffe, A. B. Tomchin, and E. N. Zhukova, *Zh. Obshch. Khim.* **39**, 78 (1969).

³⁹⁶ I. S. Ioffe, A. B. Tomchin, and E. N. Zhukova, *Zh. Obshch. Khim.* **39**, 640 (1969).



acetic anhydride gave a compound that probably was **111**.³³³ It is reported³⁹⁵ that **108** exists as the thione in the crystalline state. A wide variety of substituted analogs of **108** have also been prepared.^{58,397,398} Treatment of **112** under the same conditions that lead to the formation of **108** gave only isatin-3-semicarbazone³⁹⁶ although heating in pyridine did lead to **110**.³³³

N-methylisatin-3-semicarbazone could be cyclized to the oxo analog of **108**,³⁹⁹ but the cyclization of the thiosemicarbazone to **108** occurred much more easily.⁴⁰⁰ Similar treatment of isatin-3-semicarbazone led to **113** via ring opening of the isatin.⁴⁰⁰ In the *N*-acetyl series (**98**, R' =



³⁹⁷ Allen & Hanburys Ltd., Netherlands Patent 6,410,823 (1965); *Chem. Abstr.* **63**, 13295 (1965).

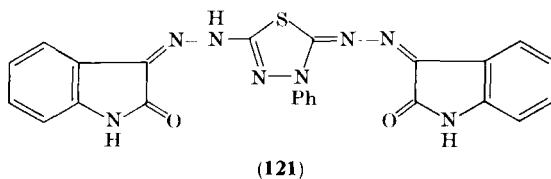
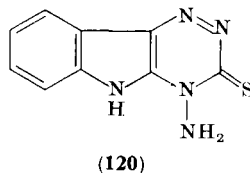
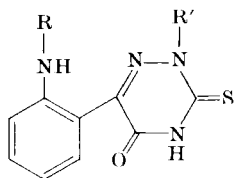
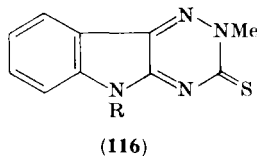
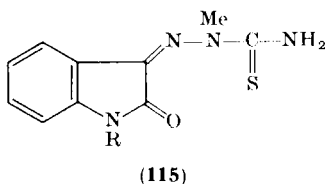
³⁹⁸ J. M. Z. Gladych, R. Hornby, J. H. Hunt, D. Jack, J. J. Boyd, R. J. Ferlauto, R. F. Haff, C. G. Kormendy, F. J. Stanfield, and R. C. Stewart, *J. Med. Chem.* **15**, 177 (1972).

³⁹⁹ A. B. Tomchin and I. S. Ioffe, *Zh. Org. Khim.* **8**, 1740 (1972).

⁴⁰⁰ I. S. Ioffe, A. B. Tomchin, and E. A. Rusakov, *Zh. Obshch. Khim.* **39**, 2345 (1969).

COMe) the cyclization, in refluxing pyridine or acetic acid, gave **114**,³³³ and the chemistry of this series has been discussed.

The thiosemicarbazones **115** underwent cyclization³⁹⁶ and ring opening⁴⁰¹ to give **116** and **117**. It is reported⁴⁰² that **113** and **117** are formed by different mechanisms in that **117** is formed from the tricyclic system while **113** is not. The analog **118** is obtained by treating isatin with potassium hydroxide and then semicarbazide^{333,403} and **119** is similarly obtained from *N*-methylisatin.³³³ Treatment of **118** and **119** with acid or heat gave **108**,³³³ while reaction of **118** with methyl iodide and sodium hydroxide followed by acid or heat gave **110**.³³³ Reaction of **105** ($R = R' = R'' = H$) with acid gave **106**, while reaction with



sodium hydroxide gave a low yield of **120** in addition to **106** and isatin azine.³⁸⁴ Reaction of **105** ($R = R' = H, R'' = \text{Ph}$) gave the thiadiazole **121**. As might be expected **98** ($R = R' = H, R'' = \text{Me}$) did not undergo cyclization but underwent ring opening with alkali.⁴⁰⁴

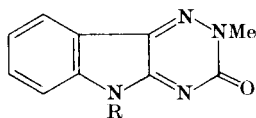
⁴⁰¹ I. S. Ioffe, A. B. Tomchin, and E. A. Rusakov, *Zh. Obshch. Khim.* **40**, 682 (1970).

⁴⁰² I. S. Ioffe and A. B. Tomchin, *Zh. Obshch. Khim.* **40**, 859 (1970).

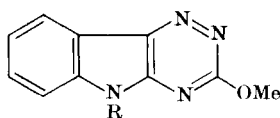
⁴⁰³ A. B. Tomchin, I. S. Ioffe, and E. A. Rusakov, *Zh. Org. Khim.* **8**, 1791 (1971).

⁴⁰⁴ A. B. Tomchin, Y. A. Kharit, and A. K. Kutsenko, *Khim. Farm. Zh.* **7**, 10 (1973).

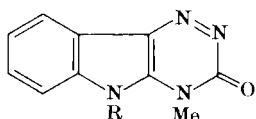
The oxo analog of **108** undergoes alkylation in alkali to give **122**,⁴⁰⁵ while alkylation of the silver salt gives **122**, **123**, and **124**.⁴⁰⁵ The amino analog can be obtained by heating the *syn*-3-guanylhyazone (**101**) of isatin with ammonia or by slowly heating the anti isomer to 250° in a



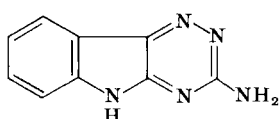
(122)



(123)



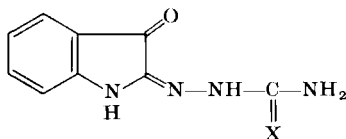
(124)



(125)

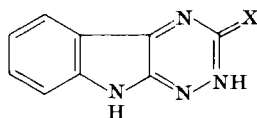
high vacuum.⁴⁰⁶ A variety of analogs of **125** have been prepared³⁹⁷ as have analogs obtained from the 3-nitroguanylhyazone of isatin-2-oxime.⁴⁰⁷

The cyclization of certain 2-substituted isatin derivatives were studied so as to compare them with the above cyclizations. Thus, isatin-2-thiosemicarbazone (**126**) and isatin-2-semicarbazone (**127**) underwent cyclization to **128** and **129** more easily than the corresponding cyclizations in the 3-series.⁴⁰⁸ As in the 3-series the sulfur compound underwent cyclization more easily than the oxygen.⁴⁰⁸ In contrast to



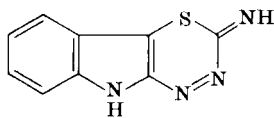
(126) X = S

(127) X = O

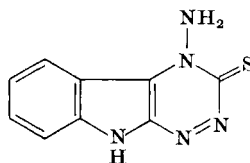


(128) X = S

(129) X = O



(130)



(131)

⁴⁰⁵ I. S. Ioffe, A. B. Tomchin, and E. N. Zhukova, *Zh. Obshch. Khim.* **39**, 2339 (1969).

⁴⁰⁶ H. King and J. Wright, *J. Chem. Soc.*, 2314 (1948).

⁴⁰⁷ F. J. Lalor and F. L. Scott, *J. Chem. Soc. C*, 1034 (1969).

⁴⁰⁸ I. S. Ioffe, A. B. Tomchin, and G. A. Shirokii, *Zh. Org. Khim.* **7**, 179 (1971).

98, which was stable in acid, **126** on treatment with hydrochloric acid gave **130**.⁴⁰⁹ Reaction of isatin-2-anil with an excess of thiocarbohydrazide gave **131**,⁴¹⁰ while an excess of isatin gave the 2,2'-analog **106**.⁴¹⁰

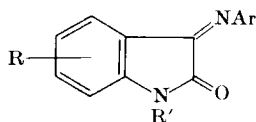
A number of additional reports have appeared.^{410a-410e}

VIII. Reactions with Amines

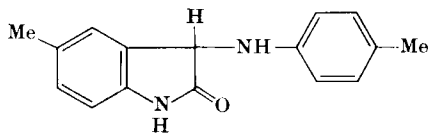
A. PRIMARY AMINES

1. Aromatic Primary Amines

A large variety of aromatic amines react with isatins to give anils (**132**).^{169,232,269,305,312,411-413} The imine from isatin and *o*-hydroxyaniline forms complexes with copper acetate and zinc iodide.⁴¹³ Reaction of these anils (**132**) with phenylhydrazine gives the isatin-3-phenylhydrazone.⁴¹¹ The imine **132** (R = 5-Me, R' = H, Ar = *p*-tolyl)



(132)



(133)

has been prepared by reaction of dichloroacetic acid with *p*-toluidine⁴¹⁴ or from 5-methylisatin and **133**.^{161,162}

Reaction of a variety of substituted isatins with *o*-phenylenediamine gives indolo[2,3-*b*]quinoxalines (indophenazines) (**134**).^{7,21,22,32,43,80,86,107,154,169,193a,207,239,415-417} Substituted *o*-phenylenediamines have also

⁴⁰⁹ A. B. Tomchin, I. S. Ioffe, and G. A. Shirokii, *Zh. Org. Khim.* **8**, 870 (1972).

⁴¹⁰ A. B. Tomchin, I. S. Ioffe, and G. A. Shirokii, *Zh. Org. Khim.* **8**, 400 (1972).

^{410a} A. B. Tomchin, I. S. Ioffe, A. I. Koltsov, and Y. V. Lepp, *Khim. Geterotsikl. Soedin.*, 503 (1974).

^{410b} A. B. Tomchin, I. S. Ioffe, and G. A. Shirokii, *Zh. Org. Khim.* **10**, 103 (1974).

^{410c} A. B. Tomchin, I. S. Ioffe, Y. V. Lepp, and T. N. Timofeeva, *Zh. Org. Khim.* **10**, 371 (1974).

^{410d} A. B. Tomchin, V. S. Dmitrukha, T. N. Timofeeva, and P. S. Pelkis, *Zh. Org. Khim.* **10**, 1519 (1974).

^{410e} A. B. Tomchin and Y. V. Lepp, *Zh. Org. Khim.* **10**, 1962 (1974).

⁴¹¹ G. B. Crippa and S. Pietra, *Gazz. Chim. Ital.* **81**, 195 (1951).

⁴¹² R. K. Grantham and O. Meth-Cohn, *Chem. Commun.*, 500 (1968).

⁴¹³ G. Manecke and J. Gauger, *Chem. Ber.* **101**, 3326 (1968).

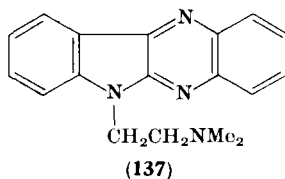
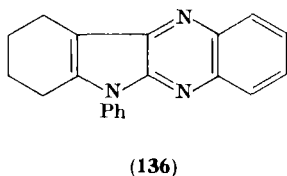
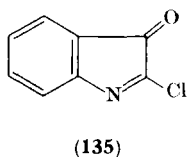
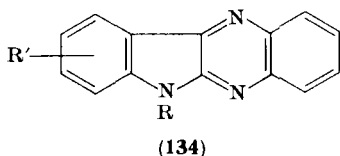
⁴¹⁴ G. B. Crippa and S. Pietra, *Gazz. Chim. Ital.* **78**, 456 (1948).

⁴¹⁵ G. M. Badger and P. J. Nelson, *J. Chem. Soc.*, 3926 (1962).

⁴¹⁶ N. P. Buu-Hoi, D. P. Hien, and G. Saint-Ruf *C.R. Acad. Sci., Ser. D* **264**, 2414 (1967).

⁴¹⁷ Y. Kidani, M. Matsuo, and H. Koike, *Yakugaku Zasshi* **90**, 54 (1970).

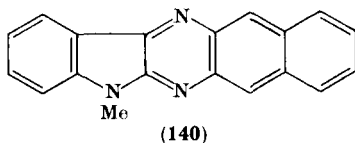
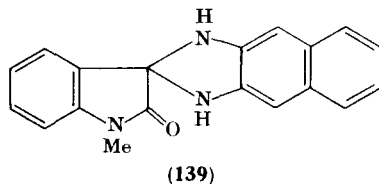
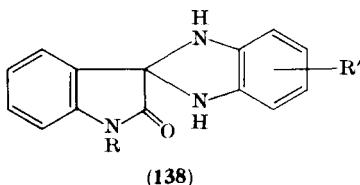
been used to give compounds of the type **134**.^{239,416-420a} In cases where unsymmetrically substituted *o*-phenylenediamines have been used, the structure has generally not been proved,^{7,239,240,416,418,419,420a,421,422} although **135** has been used in such cases to determine the structure.⁴¹⁷



The preparation of compounds of type **134** is usually carried out by simply heating the diamine and isatin; however, polyphosphoric acid has been used in some cases.^{423,424} Although **19** (R = Ph) does not react with aniline, it gives **136** with *o*-phenylenediamine.⁷⁸

A variety of reactions of indophenazines have been studied.^{32,154,415,-417,425-426a} *N,N*-Dimethylaminoethylindophenazine (**137**) has been reported to possess antimicrobial action.¹⁵⁴

In some cases, a spiro structure (**138**) is obtained instead of, or in



⁴¹⁸ N. P. Buu-Hoi and P. Jacquignon, *C.R. Acad. Sci.* **226**, 2155 (1948).

⁴¹⁹ S. K. Guha, K. D. Banerji, and K. K. Sen, *J. Indian. Chem. Soc.* **50**, 264 (1973).

⁴²⁰ G. Henseke and W. Lemke, *Chem. Ber.* **91**, 101 (1958).

^{420a} N. P. Buu-Hoi, G. Saint-Ruf, and J. C. Arcos, *Bull. Soc. Chim. Fr.*, 838 (1969).

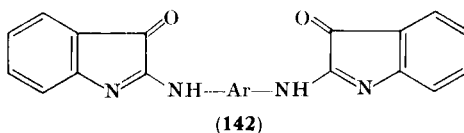
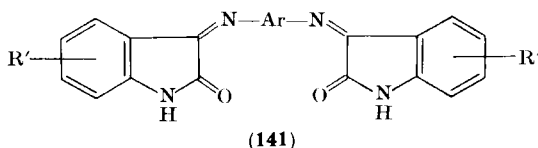
⁴²¹ N. P. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 1920 (1960).

⁴²² E. M. Gal, *Experientia* **7**, 261 (1951).

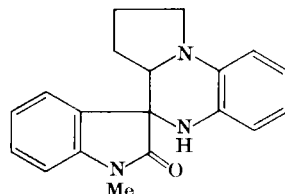
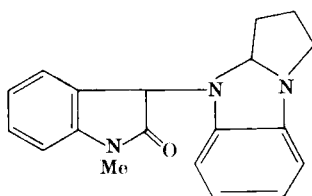
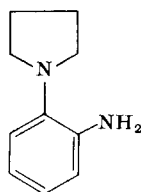
⁴²³ I. Shopov, *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk.* **3**, 47 (1970); *Chem. Abstr.* **74**, 32028 (1971).

⁴²⁴ I. Shopov and N. Popov, *J. Polym. Sci., Part A-1* **7**, 1803 (1969).

addition to, the linear structure **134**,^{239,240,420} and such a structure may actually have been obtained in another case when a hydrate of **134** was claimed.⁴²² It is possible to convert **139** to **140** by refluxing in glacial acetic acid,²³⁹ but no other such interconversions have been reported for other members of the series. A number of other aromatic diamines (not *o*-) gave **141**^{410,427,427a} on reaction with isatin, while these diamines with **135** gave **142**.^{429,430} A comparison of the infrared spectra of **141** and **142** has been made.⁴²⁸



Although *N*-methylisatin and **143** in ethanol gives the expected anil,⁴¹² reaction in acid can give **144** and **145**.⁴¹² A mechanism analogous to the Stevens rearrangement is proposed for the formation of **145**.



2. Aliphatic Primary Amines

Primary aliphatic amines are also reported to give imines of the type **132** (where Ar now is aliphatic) with isatin,^{92,170,431-433} although the

⁴²⁵ Y. Kidani, M. Matsuo, and H. Koike, *Yakugaku Zasshi* **90**, 452 (1970).

⁴²⁶ M. Matsuo, Y. Kidani, and H. Koike, *Yakugaku Zasshi* **90**, 601 (1970).

^{426a} T. Kappe and W. Lube, *Monatsh. Chem.* **102**, 781 (1971).

⁴²⁷ R. Vilceanu, B. D. Bader, M. Radulescu, and M. Marinescu, *Rev. Roum. Chim.* **18**, 1225 (1973).

^{427a} A. Jindra, *Collect Czech. Chem. Commun.* **12**, 541 (1947).

⁴²⁸ R. Bacaloglu and B. D. Bader, *Rev. Roum. Chim.* **18**, 275 (1973).

⁴²⁹ B. D. Bader and R. Vilceanu, *Rev. Roum. Chim.* **17**, 1991 (1972).

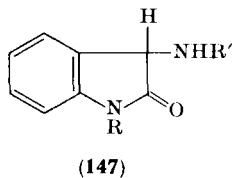
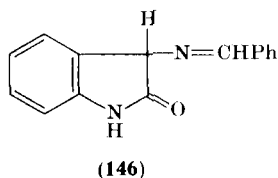
⁴³⁰ J. Reichel, B. D. Bader, and R. Vilceanu, *Rev. Roum. Chim.* **17**, 1889 (1972).

⁴³¹ F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, 209 (1954).

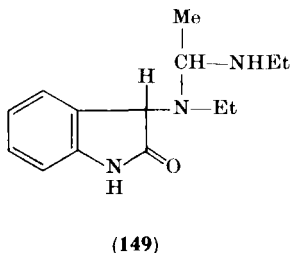
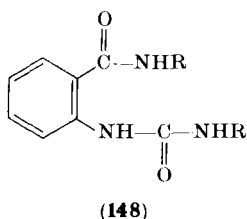
⁴³² R. M. Piccirilli and F. D. Popp, *J. Heterocycl. Chem.* **10**, 671 (1973).

⁴³³ R. M. Piccirilli and F. D. Popp, *J. Heterocycl. Chem.* **10**, 877 (1973).

tautomer **146** has been proposed, without proof, for the product from isatin and benzylamine.⁹² Reduction of these imines or reductive amination of isatin gives **147**.¹⁷⁰



When an excess of primary aliphatic amine is used with isatin, the situation becomes much more complicated.^{432,433} With a 10-fold excess of cycloalkylamines in ethanol in the presence of air, ring opening takes place to give **148** (R = cycloalkyl).⁴³² Under these same conditions other primary aliphatic amines gave purple gums which did not give crystalline products.^{432,433} Isatin-3-imines also undergo ring opening with an excess of cycloalkylamines to give **148** in which both R groups are derived from the cycloalkyl residue.⁴³² The reaction of isatin or isatin-3-imines, in the absence of a solvent, with an excess of ethylamine gives a product which is believed to be **149**.⁴³³



Isatin has been used in the Strecker degradation of α -amino acids to aldehydes,⁴³⁴⁻⁴³⁷ and in the formation of benzaldehydes from benzylamines.^{431,435,438-440} These conversions have been the subject of a review, and mechanisms have been proposed.⁴⁴¹ This formation of aldehydes from primary amines may, in part, explain some of the

⁴³⁴ E. Giovannini and P. Portmann, *Helv. Chim. Acta* **31**, 1361 (1948).

⁴³⁵ A. Schonberg, R. Moubasher, and A. Mostafa, *J. Chem. Soc.* 176 (1948).

⁴³⁶ F. G. Baddar and Z. Iskander, *Nature (London)* **167**, 1069 (1951).

⁴³⁷ F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, 203 (1954).

⁴³⁸ S. J. Angyal, P. J. Morris, R. C. Rassack, and J. A. Waterer, *J. Chem. Soc.*, 2704 (1949).

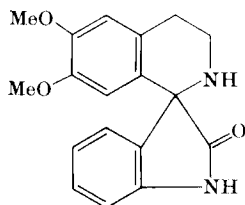
⁴³⁹ W. G. Brouwer, W. A. Craig, J. A. D. Jeffreys, and A. Munro, *J. Chem. Soc., Perkin Trans. 1*, 124 (1972).

⁴⁴⁰ A. Schonberg and R. Moubasher, *J. Chem. Soc.*, 1422 (1950).

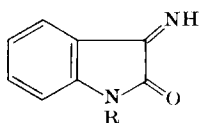
⁴⁴¹ A. Schonberg and R. Moubasher, *Chem. Rev.* **50**, 261 (1952).

results noted above in the reactions of isatin with an excess of primary aliphatic amines.

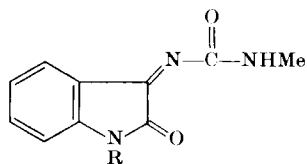
An attempt to utilize this conversion of amines into aldehydes in an isoquinoline synthesis was not successful.⁴³⁹ Instead, reaction between 2-(3,4-dimethoxyphenyl)ethylamine and isatin afforded only the spiro compound **150**.⁴³⁹ Reaction between isatin and 2-(3-hydroxy-4-methoxyphenyl)ethylamine gave a mixture of two spiro compounds, while a reaction of isatin, this amine, and benzylamine gave 6-hydroxy-7-methoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline.⁴³⁹



(150)

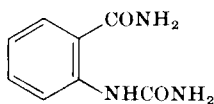


(151)

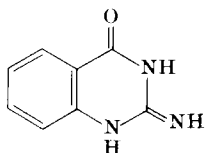


(152)

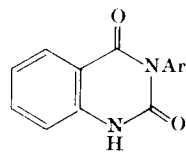
Isatin and *N*-methylisatin can be reacted with ammonia to give an imine (**151**). With methyl isocyanate these imines give **152** ($R = \text{CONHMe}$ and Me , respectively).¹²³ Oxidation of the imine **151** ($R = \text{H}$) with hydrogen peroxide in aqueous ammonia gave **153** while a similar oxidation of isatin gave only anthranilic acid.⁴⁴² This ring opening can



(153)



(154)



(155)

be compared with the one noted above for isatin and an excess of cycloalkylamines.⁴³² A similar ring opening appears to be involved when isatin and ammonia are reacted for three months in sunlight to give **154**⁴⁴³ and when **132** ($R = R' = \text{H}$) is oxidized with alkaline peroxide to give **155**.⁴⁴⁴

The structure of isamic acid, $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}_3 \cdot \text{H}_2\text{O}$, obtained from ammonia and isatin or from sodium isatoate and **151** ($R = \text{H}$) has been studied for some time.^{445,446} In 1967 structure **156** was suggested for

⁴⁴² G. Jacini, *Gazz. Chim. Ital.* **72**, 510 (1942).

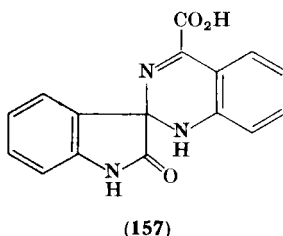
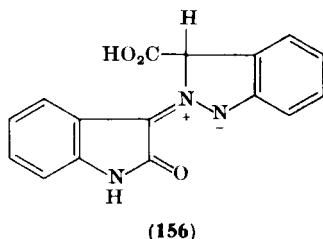
⁴⁴³ S. Capuano and L. Giammanco, *Gazz. Chim. Ital.* **86**, 126 (1956).

⁴⁴⁴ G. Jacini, *Gazz. Chim. Ital.* **73**, 85 (1943).

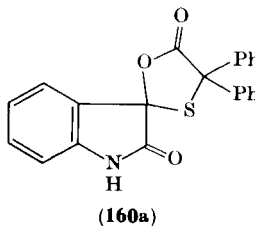
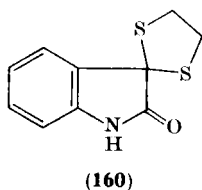
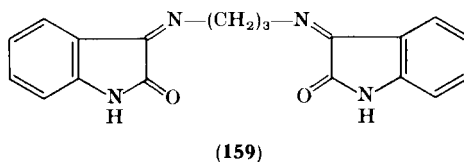
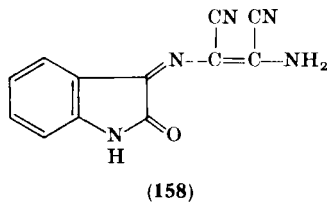
⁴⁴⁵ G. Jacini, *Gazz. Chim. Ital.* **73**, 306 (1943).

⁴⁴⁶ G. Jacini, *Gazz. Chim. Ital.* **77**, 295 (1947).

isamic acid,⁴⁴⁷ but in 1969 this structure was challenged and the more reasonable structure **157** was proposed.⁴⁴⁸



Although diaminomaleonitrile reacts with only 1 mole of isatin to give **158**,^{449,450} 1,3-diaminopropane reacts to give **159**.⁴⁵¹ The reaction of other diaminoalkanes appears to be more complicated.⁴⁵² In related reactions 2-aminoethylthiol,⁴⁵³ 3-aminopropylthiol,⁴⁵⁴ and ethanedithiol⁴⁵⁵ react to give spiro compounds, such as **160**. Raney nickel and **160** leads to oxindole and in the presence of alcohols to 3-alkyloxindoles.⁴⁵⁵ Mercaptodiphenylacetic acid and isatin in the presence of *p*-toluenesulfonic acid give **160a**.^{455a}



⁴⁴⁷ P. DeMayo and J. J. Ryan, *Chem. Commun.*, 88 (1967).

⁴⁴⁸ G. F. Field, *Chem. Commun.*, 886 (1969).

⁴⁴⁹ H. Brederick and G. Schmotzer, *Justus Liebigs Ann. Chem.* **600**, 95 (1956).

⁴⁵⁰ F. D. Popp, *J. Heterocycl. Chem.* **11**, 79 (1974).

⁴⁵¹ R. H. McDougall and S. H. Malik, *J. Chem. Soc. C*, 2044 (1969).

⁴⁵² F. D. Popp and L. Maier, unpublished results.

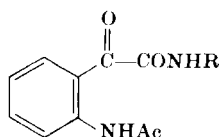
⁴⁵³ M. Wolf and A. A. Mascitti, U.S. Patent 3,458,525 (1969); *Chem. Abstr.* **72**, 21715 (1970).

⁴⁵⁴ M. Wolf, U.S. Patent 3,314,951 (1967); *Chem. Abstr.* **67**, 90819 (1967).

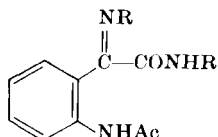
⁴⁵⁵ E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.* **80**, 5575 (1958).

^{455a} A. Romo de Vivar and J. Romo, *J. Org. Chem.* **24**, 1490 (1959).

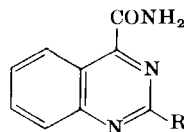
Notwithstanding an earlier report,⁴⁵⁶ *N*-acetylisatin does not appear to react with primary amines to give 3-imines. Instead ring opening takes place and **161** is obtained.⁴⁵⁷ When an excess of the primary amine reacts with *N*-acetylisatin, **162**, which can also be obtained by reaction of **161** with the amine, is obtained.⁴⁵⁷ A similar ring opening takes place between *N*-acylisatins and ammonia⁴⁵⁸ and between *N*-



(161)



(162)

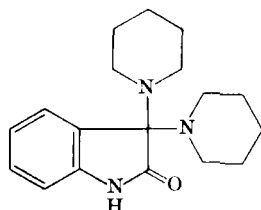


(163)

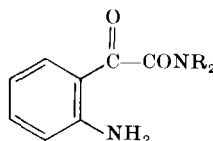
acylisatins and alcohols.^{458,459} An excess of ammonia with *N*-acylisatins^{164,458} or with **161** ($R = H$)⁴⁵⁸ leads to the quinazolines **163**.

B. SECONDARY AMINES

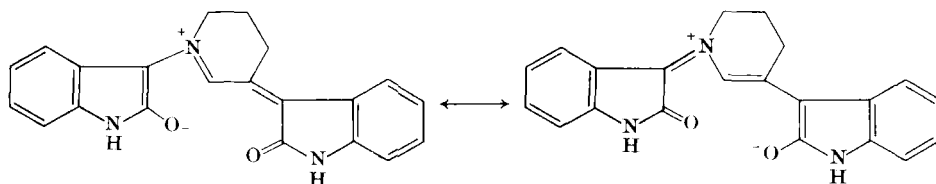
Isatin reacts with secondary heterocyclic amines to give 3,3-diamino-oxindoles such as, for example, **164**.⁴⁶⁰⁻⁴⁶² Such compounds can also be prepared by reaction of secondary amines with isatin-3-anils.⁴⁶¹ These secondary amines can also react with isatin with ring opening to give **165**.⁴⁶¹



(164)



(165)



(166)

⁴⁵⁶ F. Parisi, *J. Amer. Chem. Soc.* **75**, 3848 (1953).

⁴⁵⁷ F. D. Popp and R. M. Piccirilli, *J. Heterocycl. Chem.* **8**, 473 (1971).

⁴⁵⁸ F. J. Meyer, *Chem. Ber.* **99**, 3060 (1966).

⁴⁵⁹ R. Johnstone and J. R. Price, *Aust. J. Chem.* **7**, 209 (1954).

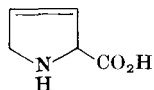
⁴⁶⁰ Kodak S.A., Belgian Patent 533,980 (1960); *Chem. Abstr.* **55**, 11157 (1961).

⁴⁶¹ A. W. Johnson and D. J. McCaldin, *J. Chem. Soc.*, 3470 (1957).

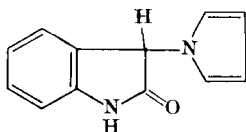
⁴⁶² W. R. Lawton, Belgian Patent 655, 926 (1965); *Chem. Abstr.* **65**, 5577 (1966).

Reaction of **164** with acetic anhydride, reaction of isatin with L-pipecolic acid, or reaction of pyrrolidine with isatin in acetic anhydride gives a substance known as isatin blue. Proline and isatin give the same product and the blue color is the basis of a color test for such compounds.⁴⁶³⁻⁴⁶⁸ The structure **166** has been proposed for isatin blue,⁴⁶¹ and other related compounds have also been prepared.⁴⁶¹

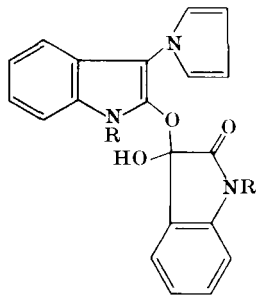
In contrast to proline, 3,4-dehydro-DL-proline (**167**) does not give a color with isatin.⁴⁶⁹ The reaction proceeds to give **168** and the mechanism of formation has been discussed.⁴⁶⁹ Both *cis*- and *trans*-4-chloro-L-proline⁴⁶⁹ and Δ^3 -pyrroline⁴⁷⁰ also react with isatin to give **168**. A



(167)



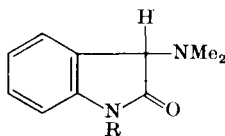
(168)



(169)

variety of 5- and 7-substituted isatins react with **167** to give analogs of **168**.¹⁴⁷ Reaction of **167** with N-substituted isatins in a buffer-alcohol mixture gave analogs of **168**, but in buffer alone the reaction proceeded to give **169**.¹⁴⁷

Although reductive amination of isatin with dimethylamine did not succeed, reaction of N-substituted isatins with dimethylamine in the presence of palladium on carbon and hydrogen gave **170**.¹⁷⁰



(170)

⁴⁶³ D. J. McCaldin, *Can. J. Chem.* **38**, 1229 (1960).

⁴⁶⁴ F. N. Boctor, *Anal. Biochem.* **43**, 66 (1971).

⁴⁶⁵ R. P. Morozova, *Ukr. Biokhim. Z.* **37**, 290 (1965); *Chem. Abstr.* **63**, 3294 (1965).

⁴⁶⁶ J. Noworytko and M. Sarnecka-Keller, *Acta Biochim. Pol.* **2**, 91 (1955); *Chem. Abst.* **50**, 16531 (1956).

⁴⁶⁷ A. Saifer and I. Oreskes, *Science* **119**, 124 (1954).

⁴⁶⁸ A. A. Titaev, *Lab. Delo*, 589 (1970); *Chem. Abstr.* **74**, 39034 (1971).

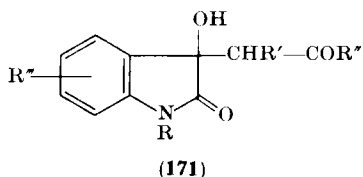
⁴⁶⁹ C. B. Hudson and A. V. Robertson, *Aust. J. Chem.* **20**, 1511 (1967).

⁴⁷⁰ C. B. Hudson and A. V. Robertson, *Tetrahedron Lett.*, 4015 (1967).

IX. Condensations Involving Carbon at C-3

A. REACTIONS LEADING TO 3-HYDROXY-3-SUBSTITUTED OXINDOLES

Under mildly basic conditions, such as with piperidine or diethylamine as catalyst, isatins condense with a wide variety of ketone to give compounds of the type **171**.^{144,145,150,169,232,471-490} These compounds have frequently been used to prepare substituted tryptamines^{476,484,485,487} and also some 9H-pyridazino[3,4-b]indole



derivatives.^{479,490} In the case of isatin and propiophenone, two diastereoisomers are obtained.^{483,489} Although mixtures are obtained from methyl ethyl ketone and methyl *n*-propyl ketone, other methyl alkyl ketones condense at the methyl rather than the methylene group.⁴⁷³ It is possible to condense acetone and cyclohexanone⁴⁹⁰ with two moles of isatin.

⁴⁷¹ F. A. Al-Tai, A. M. El-Abbady, and A. S. Al-Tai *U.A.R. J. Chem.* **10**, 339 (1967).

⁴⁷² P. Bamfield, A. W. Johnson, and A. S. Katner, *J. Chem. Soc. C*, 1028 (1966).

⁴⁷³ J. Bergman, *Tetrahedron* **27**, 1167 (1971).

⁴⁷⁴ J. W. Cornforth, R. H. Cornforth, C. E. Dalglish, and A. Neuberger, *Biochem. J.* **48**, 591 (1951).

⁴⁷⁵ S. David and M. C. Doucet, *Bull. Soc. Chim. Fr.*, 2152 (1967).

⁴⁷⁶ C. S. Franklin and A. C. White, *J. Chem. Soc.*, 1335 (1963).

⁴⁷⁷ C. S. Franklin and A. C. White, British Patent 974,894 (1964); *Chem. Abstr.* **62**, 9110 (1965).

⁴⁷⁸ K. G. Holden, U.S. Patent 3,631,177 (1971).

⁴⁷⁹ G. Kobayashi and S. Furukawa, *Chem. Pharm. Bull.* **12**, 1129 (1964).

⁴⁸⁰ R. E. Lutz and C. T. Clark, *J. Org. Chem.* **25**, 193 (1960).

⁴⁸¹ N. N. Maxim and S. Petrescu, *C.R. Acad. Sci. Roum.* **8**, 65 (1946); *Chem. Abstr.* **43**, 1411 (1949).

⁴⁸² S. Pietra and G. Tacconi, *Gazz. Chim. Ital.* **89**, 2304 (1959).

⁴⁸³ S. Pietra and G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **15**, 451 (1960).

⁴⁸⁴ S. Pietra and G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **16**, 483 (1961).

⁴⁸⁵ S. Pietra and G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **13**, 893 (1958).

⁴⁸⁶ S. Pietra and G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **16**, 492 (1961).

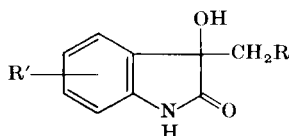
⁴⁸⁷ G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **20**, 891 (1965).

⁴⁸⁸ G. Tacconi, *Farmaco (Pavia) Ed. Sci.* **20**, 902 (1965).

⁴⁸⁹ S. Pietra and G. Tacconi, *Gazz. Chim. Ital.* **92**, 1422 (1962).

⁴⁹⁰ F. D. Popp, unpublished results.

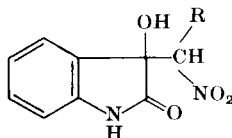
Other similar reagents such as nitroalkanes,^{152,491} methyl acetimidate $\text{CH}_3\text{C}(=\text{NH})\text{OCH}_3$,⁴⁹² lactonitrile and dibenzylamine,⁴⁹³ 2-methylpyridine,⁴⁹⁴ and 4-alkylpyridines^{494a} gave **172–175**, respectively. Although active methylene compounds generally give rise to isatylidene derivatives, diethyl malonate⁴⁹⁵ and ethyl cyanoacetate¹⁴⁴ have been reported to give 3-substituted-3-hydroxyoxindoles.



(173) $\text{R} = \text{C}(=\text{NH})\text{OMe}$

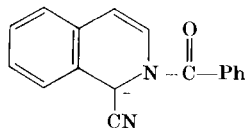
(174) $\text{R} = \text{CH}(\text{CN})\text{N}(\text{CH}_2\text{Ph})_2$

(175) $\text{R} = 2\text{- or } 4\text{-pyridyl}$

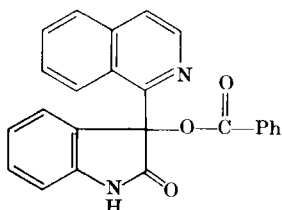


(172)

Reaction of the Reissert compound anion **176** with isatin gave the ester **177**.⁴⁹⁶



(176)



(177)

Isatin and its derivatives have reacted with both aryl and alkyl Grignard reagents to give 3-alkyl (or aryl) dioxindoles (**178**).^{232,497–500} Use of an excess of phenylmagnesium bromide with *N*-benzyl⁵⁰¹ and

⁴⁹¹ G. Tacconi and S. Pietra, *Farmaco (Pavia) Ed. Sci.* **18**, 409 (1963).

⁴⁹² W. Ried and F. Kohlhaas, *Justus Liebigs Ann. Chem.* **701**, 139 (1967).

⁴⁹³ A. Meyer and P. H. Payot, S. African Patent 68 07,093 (1969); *Chem. Abstr.* **72**, 43441 (1970).

⁴⁹⁴ A. M. Akkerman and H. Veldstra, *Rec. Trav. Chim.* **73**, 629 (1954).

^{494a} G. Tacconi, S. Pietra, and M. Zaglio, *Farmaco (Pavia) Ed. Sci.* **20**, 470 (1965).

⁴⁹⁵ G. L. Papayan, *Arm. Khim. Zh.* **22**, 457 (1969); *Chem. Abstr.* **71**, 70439 (1969).

⁴⁹⁶ F. D. Popp, C. W. Klinowski, R. Piccirilli, D. H. Purcell, and R. F. Watts, *J. Heterocycl. Chem.* **8**, 313 (1971).

⁴⁹⁷ H. E. Baumgarten and P. L. Creger, *J. Amer. Chem. Soc.* **82**, 4634 (1960).

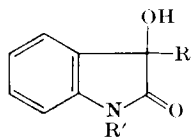
⁴⁹⁸ J. Bergman, *Acta Chem. Scand.* **25**, 1277 (1971).

⁴⁹⁹ M. C. Bettembourg and S. David, *Bull. Soc. Chim. Fr.*, 772 (1962).

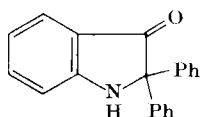
⁵⁰⁰ B. Mills and K. Schofield, *J. Chem. Soc.*, 558 (1961).

⁵⁰¹ S. Sarel and J. T. Klug, *Isr. J. Chem.* **2**, 143 (1964).

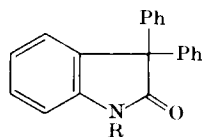
N-methylisatin^{502,503} has been reported to give the *N*-substituted 2,2-diphenylindoxyl (**179**) and 3,3-diphenyloxindole (**180**) rather than epoxides as claimed¹ earlier. Phenyllithium and isatin also give rise to **178** ($R' = H$, $R = Ph$).⁵⁰⁴ Zinc and ethyl bromoacetate also give products of the type **178**.^{150,245,492}



(178)

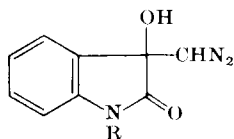


(179)

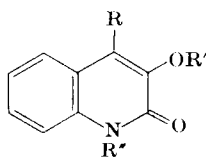


(180)

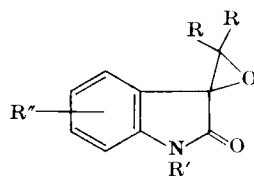
Isatin and *N*-substituted isatins react with diazoalkanes to give a variety of products. Simple adducts of the type **181** have been obtained when *N*-substituted isatins react with methanol-free diazomethane and are reported to lose nitrogen and react further in methanol.⁵⁰⁵ Such adducts have also been reported in other cases.^{196,506-508} Ring enlargement to quinolones (**182**; R is the R in $RCHN_2$ and R' is usually OH but sometimes OMe from diazomethane) frequently occurs.^{123,196,506-509} Finally, epoxides of the type **183** have sometimes been obtained from the diazoalkane reaction.^{123,249,507,510} With diphenyldiazomethane, ring expansion does not take place and **183** ($R = Ph$) is the only



(181)



(182)



(183)

product. Hydrolysis of **183** ($R = Ph$, $R' = H$, $R'' = 5-Me$) with hydrochloric acid gave isoindigo.²⁴⁹ Isatin with an excess of diphenyldiazomethane for an extended reaction time gave **183** ($R = Ph$, $R' =$

⁵⁰² W. C. Sumpter and W. W. Hunt, *Trans. Kentucky Acad. Sci.* **17**, 78 (1956); *Chem. Abstr.* **51**, 3560 (1957).

⁵⁰³ B. Witkop and A. Ek, *J. Amer. Chem. Soc.* **73**, 5664 (1951).

⁵⁰⁴ J. M. Bruce, *J. Chem. Soc.*, 2366 (1959).

⁵⁰⁵ B. Eistert and O. Ganster, *Chem. Ber.* **104**, 78 (1971).

⁵⁰⁶ B. Eistert and G. Borggreffe, *Justus Liebigs Ann. Chem.* **718**, 142 (1968).

⁵⁰⁷ B. Eistert and H. Selzer, *Chem. Ber.* **96**, 1234 (1963).

⁵⁰⁸ M. Regitz, W. Disteldorf, V. Eckstein, and B. Weber, *Tetrahedron Lett.*, 3979 (1972).

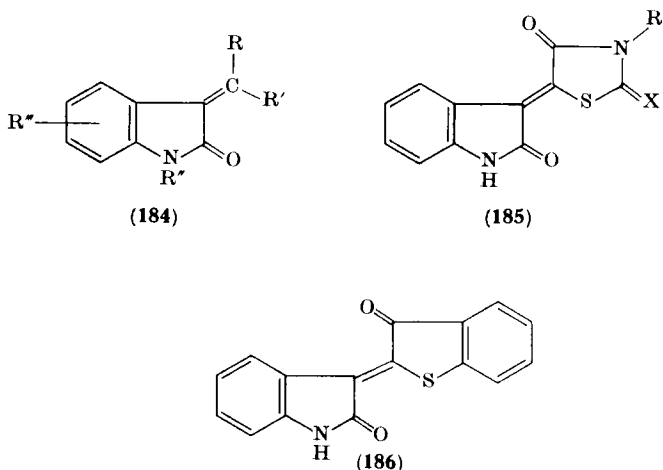
⁵⁰⁹ B. Eistert and H. Selzer, *Z. Naturforsch. B* **17**, 202 (1962).

⁵¹⁰ A. Schonberg and K. Junghaus, *Ber.* **96**, 3328 (1963).

CHPh₂, R'' = H), which was oxidized by sodium dichromate-acetic acid to *N*-(diphenylmethyl)isatin.⁵¹⁰

B. REACTIONS LEADING TO ISATYLIDENE DERIVATIVES

Compounds of the type **171** can generally be easily dehydrated and many reactions of isatins lead directly to isatylidene derivatives. Use of active methylene compounds such as malononitrile⁵¹¹ and cyanoacetate^{5,28,144,161,512,513} gave compounds of the type **184**. Various 4-thiazolidones have been condensed with isatin, generally under acidic conditions, to give **185**.⁵¹⁴⁻⁵¹⁸ Similar type compounds (**186**) have been obtained from thianaphthenes and isatin using acetic acid.⁵¹⁹⁻⁵²⁴ These compounds (**186**) have been used as dyes. Other heterocyclic ketones



⁵¹¹ L. Capuano, V. Diehl, and W. Ebner, *Chem. Ber.* **105**, 3407 (1972).

⁵¹² J. Harley-Mason and R. F. J. Ingleby, *J. Chem. Soc.*, 3639 (1958).

⁵¹³ R. G. Taborsky and W. M. McIsaac, *J. Med. Chem.* **7**, 135 (1964).

⁵¹⁴ B. Das and M. V. Roat, *J. Sci. Ind. Res. Sect. B* **14**, 16 (1955).

⁵¹⁵ R. P. Rao, *Chem. Ber.* **92**, 2600 (1959).

⁵¹⁶ R. P. Rao, *J. Sci. Ind. Research, Sect. B* **19**, 29 (1960).

⁵¹⁷ R. P. Rao, *Proc. Nat. Acad. Sci., India, Sect. A* **30**, 181 (1961).

⁵¹⁸ R. P. Rao and S. Raj, *J. Ind. Chem. Soc.* **50**, 366 (1973).

⁵¹⁹ Ciba, Ltd., British Patent 607,608 (1948); *Chem. Abstr.* **43**, 9470 (1949).

⁵²⁰ S. K. Guha and J. N. Chatterjea, *J. Indian Chem. Soc.* **24**, 473 (1947).

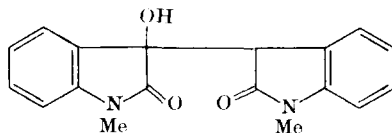
⁵²¹ S. K. Guha, J. N. Chatterjea, and A. K. Mitra, *Chem. Ber.* **94**, 2295 (1961).

⁵²² K. Hoelzle and E. Kambli, U.S. Patent 2,453,225 (1948); *Chem. Abstr.* **43**, 7706 (1949).

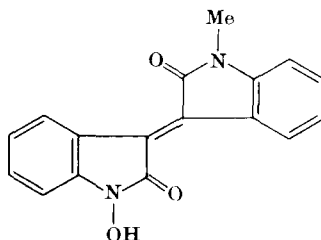
⁵²³ C. Shinomiya and K. Yamada, *Kogyo Kagaku Zasshi* **67**, 146 (1964); *Chem. Abstr.* **61**, 5819 (1964).

⁵²⁴ A. K. Sinha, *J. Indian Chem. Soc.* **31**, 463 (1954).

also react to give compounds of the type 184.⁵²⁵⁻⁵²⁹ The 2-isatyridene analogs of **186** have been obtained by using **135** in place of isatin.^{519,522} It is of interest to contrast the reaction of *N*-methylisatin and *N*-



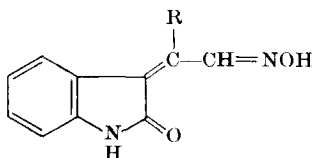
(187)



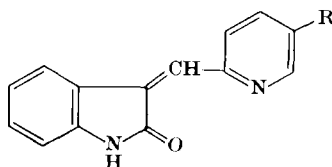
(188)

methyloxindole under basic conditions¹⁴⁴ and *N*-methylisatin and *N*-hydroxyoxindole under acidic conditions.⁵²⁵ In the former case **187** is obtained, and in the latter **188**.

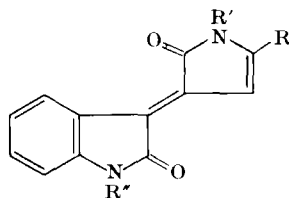
A number of aliphatic aldoximes react with isatin to give **189**.⁴⁸⁸ Although isatin and 2-methylpyridine give mainly **175** and only a small amount of **190** ($R = H$), use of 6-methylnicotinic acid⁴⁹⁴ and its ester⁴⁷² gave only **190** ($R = CO_2H$ and CO_2Et , respectively). Reaction



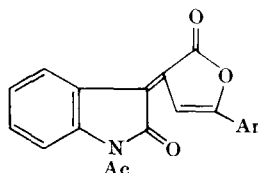
(189)



(190)



(191)



(191a)

⁵²⁵ L. Capuano and W. Ebner, *Chem. Ber.* **102**, 3691 (1969).

⁵²⁶ J. A. Ballantine, R. J. S. Beer, D. J. Crutchley, G. M. Dodd, and D. R. Palmer, *J. Chem. Soc.*, 2292 (1960).

⁵²⁷ F. E. King, T. J. King, and G. B. Thompson, *J. Chem. Soc.*, 552 (1948).

⁵²⁸ G. Stefanovic and S. Mialilovic, *Glas. Khem. Drushtva, Beograd* **22**, 459 (1959); *Chem. Abstr.* **56**, 3442 (1962).

⁵²⁹ C. B. Barrett, R. J. S. Beer, G. M. Dodd, and A. Robertson, *J. Chem. Soc.*, 4810 (1957).

of isatin or *N*-methylisatin with 3-benzoylpropionamide or 4-(3-indolyl)-*N*-methyl-4-oxobutyramide under acidic conditions gave condensation and cyclization to **191**.⁵²⁶ A similar product (**191**, R = Ph, R' = Me) was also obtained from isatin and *N*-methylisatin and 2-hydroxy-1-methyl-5-oxo-2-phenylpyrrolidine.⁵²⁶ Isatin and β -aroylpropionic acids under Perkin conditions gave butenolides (**191a**).^{529a}

The Wittig reaction and its various modifications have been used to prepare **184** (R = H; R' = CO₂Et,^{150,160,530-532} R' = Ph,⁵³³ or R' = CN¹⁶⁰).

The literature contains many transformations of compounds of the type **184** and the 2-isatyliene analogs of **184**; such compounds are frequently prepared from oxindoles⁵³³⁻⁵³⁸ and indoxyls,^{539,540} rather than from isatins.

C. MISCELLANEOUS CONDENSATIONS

Isatins condense with benzene,⁵⁴¹ alkylbenzenes,⁵⁴¹ and phenols^{37,55,542} under acidic conditions to give **192**. Hydroquinone and *N*-methylisatin with sulfuric-acetic acid gave **193**.⁵⁵ Pyrroles⁵⁴³ and indoles^{498,543} also condense with isatin under acidic⁵⁴³ or basic⁴⁹⁸ conditions.

The well-known indophenin¹ has now been obtained from isatin and thiophene using polyphosphoric acid.⁵⁴⁴

Condensation of *N*-methylisatin, glyoxal bisulfite, and sodium

^{529a} A. M. El-Abbady, M. A. Omara, and N. G. Kandil, *Rev. Roum. Chem.* **19**, 79 (1974).

⁵³⁰ R. L. Autrey and F. C. Tahk, *Tetrahedron* **24**, 3337 (1968).

⁵³¹ H. A. Brandman, *J. Heterocycl. Chem.* **10**, 383 (1973).

⁵³² J. Hollowood, British Patent 1,239,553 (1971); *Chem. Abstr.* **75**, 98446 (1971).

⁵³³ R. Hodges, J. S. Shannon, W. D. Jamieson, and A. Taylor, *Can. J. Chem.* **46**, 2189 (1968).

⁵³⁴ W. C. Anthony, *J. Org. Chem.* **31**, 77 (1966).

⁵³⁵ G. Desimoni, G. Tacconi, and F. Marinone, *Gazz. Chim. Ital.* **98**, 1301 (1968).

⁵³⁶ C. G. Richards and M. S. F. Ross, *Tetrahedron Lett.*, 4391 (1968).

⁵³⁷ G. Tacconi, A. Gamba, F. Marinone, and G. Desimoni, *Tetrahedron* **27**, 561 (1971).

⁵³⁸ G. Tacconi and F. Marinone, *Ric. Sci.* **38**, 1239 (1968).

⁵³⁹ M. Hooper and W. N. Pitkethly, *J. Chem. Soc., Perkin Trans. 1*, 1607 (1972).

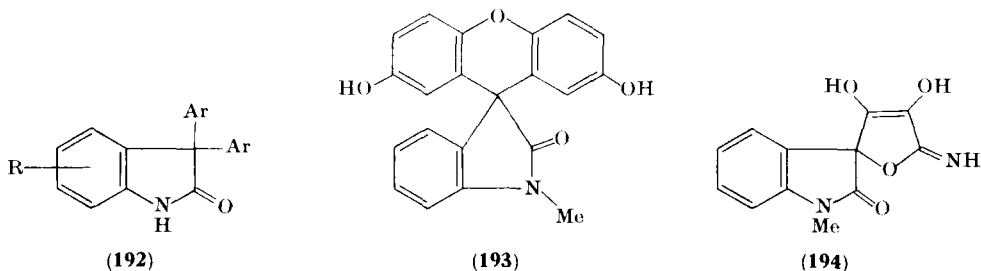
⁵⁴⁰ W. I. O'Sullivan and E. J. Rothery, *Chem. Ind. (London)*, 849 (1972).

⁵⁴¹ J. Wegmann and H. Dahn, *Helv. Chim. Acta* **29**, 415 (1946).

⁵⁴² K. Steinruck, German Patent 824,203 (1951); *Chem. Abstr.* **49**, 7004 (1955).

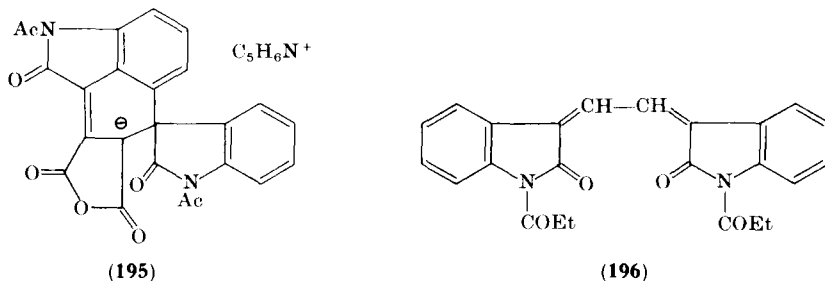
⁵⁴³ G. Muller, *J. Prakt. Chem.* **4**, 179 (1957).

⁵⁴⁴ I. Shopov and C. Vodenicharov, *J. Macromol. Sci., Chem.* **4**, 1627 (1970).



cyanide, in aqueous sodium carbonate followed by neutralization, gave the tetronimide **194**.^{545,546}

Isatin, acetic anhydride, and pyridine gave a purple condensation product **195**.⁵⁴⁷ Replacement of the acetic anhydride by propionic anhydride caused the reaction to make a different path, and three



geometric isomers of **196** were obtained.⁵⁴⁸ *N*-Propionylisatin also gave **196** and *N*-acetylisatin was converted into the *N*-acetyl analog of **196**.⁵⁴⁸

X. Pfitzinger and Related Reactions

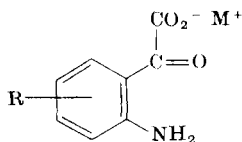
As was noted in Section IX,A, isatin reacts with ketones under mildly basic conditions to give **171**. Under stronger basic conditions, such as concentrated sodium or potassium hydroxide, the reaction takes a completely different course. The isatin undergoes ring opening in the strong base and the alkali isatate (**197**) condenses with a ketone, such as **198**, to give a quinoline-4-carboxylic acid (a cinchoninic acid) (**199**). A detailed discussion of the scope of the Pfitzinger reaction is

⁵⁴⁵ R. G. Amiet, F. W. Eastwood, and I. D. Rae, *Chem. Commun.*, 1614 (1971).

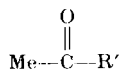
⁵⁴⁶ R. G. Amiet, F. W. Eastwood, and I. D. Rae, *Aust. J. Chem.*, **25**, 1473 (1972).

⁵⁴⁷ J. A. Ballantine, A. W. Johnson, and A. S. Katner, *J. Chem. Soc.*, 3323 (1964).

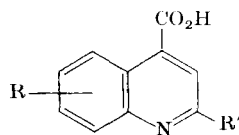
⁵⁴⁸ A. W. Johnson and A. S. Katner, *J. Chem. Soc.*, 1455 (1965).



(197)



(198)



(199)

beyond the scope of this review, but an attempt will be made to include a description of most of the examples.

Methyl ketones (198) have given rise to a wide variety of compounds of the type 199.^{16,30,32,61,207,208,214,481,549-570b} If ammonium hydroxide is used as the base, the amide of 199 is obtained,^{12,570a} Use of MeC(=NH)OEt with isatin gave the amide of 199 (R' = OEt).⁵⁷¹

Ketones of the type 200 (where R is not CH₃ or CH₂) react with isatin to give cinchoninic acids of the type 201.^{557,572-593} In a number of

⁵⁴⁹ V. Ettel and Z. J. Allan, *Chem. Listy* **46**, 249 (1952).

⁵⁵⁰ A. S. Azaryan, S. A. Avetyan, M. A. Kaldrikyan, and M. A. Iradyan, *Sin. Geterotsikl. Soedin.*, 61 (1972); *Chem. Abstr.* **79**, 146350 (1973).

⁵⁵¹ R. F. Brown, *J. Amer. Chem. Soc.* **68**, 2705 (1946).

⁵⁵² R. J. Bass, *Chem. Ind. (London)*, 848 (1973).

⁵⁵³ E. R. Buchman, H. Sargent, T. C. Myers, and D. R. Howton, *J. Amer. Chem. Soc.* **68**, 2710 (1946).

⁵⁵⁴ N. P. Buu-Hoi and P. Cagniant, *Rec. Trav. Chim.* **64**, 214 (1945).

⁵⁵⁵ N. P. Buu-Hoi and P. Cagniant, *Bull. Soc. Chim. Fr.*, 134 (1946).

⁵⁵⁶ N. P. Buu-Hoi and R. Royer, *J. Chem. Soc.*, 106 (1948).

⁵⁵⁷ N. P. Buu-Hoi, R. Royer, N. D. Xuong, and P. Jacquignon, *J. Org. Chem.* **18**, 1209 (1953).

⁵⁵⁸ A. L. Gershuns and P. Y. Pustovar, *Khim. Geterotsikl. Soedin.*, 239 (1973).

⁵⁵⁹ J. S. Gillespie, R. J. Rowlett, and R. R. Davis, *J. Med. Chem.* **11**, 425 (1968).

⁵⁶⁰ H. Gilman, L. Tolman and S. P. Massie, *J. Amer. Chem. Soc.* **68**, 2399 (1946).

⁵⁶¹ A. L. Gershuns, A. N. Brizitskaya, and P. Y. Pustovar, *Khim. Geterotsikl. Soedin.*, 1536 (1973).

⁵⁶² H. R. Henze and D. W. Carroll, *J. Amer. Chem. Soc.* **76**, 4580 (1954).

⁵⁶³ R. E. Lutz, *J. Amer. Chem. Soc.* **68**, 1813 (1946).

⁵⁶⁴ N. Okuda, *J. Pharm. Soc. Jap.* **71**, 1275 (1951).

⁵⁶⁵ M. H. Palmer and R. S. McIntyre, *J. Chem. Soc. B*, 539 (1969).

⁵⁶⁶ V. Parrini, *Gazz. Chim. Ital.* **88**, 24 (1958).

⁵⁶⁷ G. Y. Sarkis, *J. Chem. Eng. Data* **17**, 388 (1972).

⁵⁶⁸ M. N. Semtsova, P. L. Trakhtenberg, A. E. Lipkin, and T. B. Ryskina, *Khim. Farm. Zh.* **7**, 13 (1973).

⁵⁶⁹ I. Shopov and N. Kassabova, *Izv. Otd. Khim. Nauki. Bulg. Akad. Nauk.* **4**, 619 (1971).

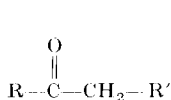
⁵⁷⁰ L. V. Thoi, *Ann. Chim. (Paris)* **10**, 35 (1955).

^{570a} S. A. Avetyan, A. S. Azaryan, and A. A. Aroyan, *Arm. Khim. Zh.* **26**, 763 (1973); *Chem. Abstr.* **80**, 70666 (1974).

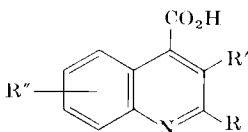
^{570b} J. Novotny, C. H. Collins, and F. W. Starks, *J. Pharm. Sci.* **63**, 1264 (1974).

⁵⁷¹ A. Kei, K. Onami, H. Fukumi, and H. Matsushima, Japan Patent 72 37,187 (1972); *Chem. Abstr.* **78**, 16060 (1973).

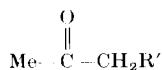
cases methyl ketones of the type **202** undergo condensation at the methylene group rather than the methyl group to give **201** ($R =$



(200)



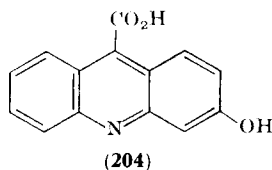
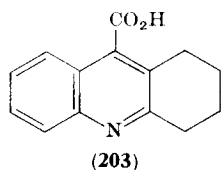
(201)



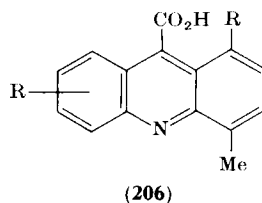
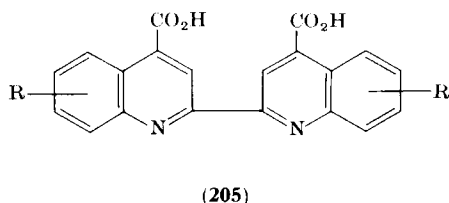
(202)

CH_3).^{556,565,594-598} The factors that influence whether **199** or **201** is obtained have been discussed.^{556,565,589,597}

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- ⁵⁷² B. I. Ardashev, A. S. Zarifyan, and G. G. Glukhovets, *Khim. Geterotsikl. Soedin.*, 525 (1972).
- ⁵⁷³ N. P. Buu-hoi, *J. Chem. Soc.*, 2882 (1949).
- ⁵⁷⁴ N. P. Buu-Hoi and P. Cagniant, *Bull. Soc. Chim. Fr.*, 123 (1946).
- ⁵⁷⁵ N. P. Buu-Hoi and Nguyen-Hoan, *Rec. Trav. Chim.* **67**, 309 (1948).
- ⁵⁷⁶ N. P. Buu-Hoi and R. Royer, *Bull. Soc. Chim. Fr.*, 374 (1946).
- ⁵⁷⁷ N. P. Buu-Hoi and R. Royer, *Bull. Soc. Chim. Fr.*, 820 (1947).
- ⁵⁷⁸ N. P. Buu-Hoi, M. Sy, and J. Riche, *J. Org. Chem.* **22**, 668 (1957).
- ⁵⁷⁹ P. Cagniant and A. Deluzarche, *C. R. Acad. Sci.* **225**, 455 (1947).
- ⁵⁸⁰ P. Cagniant and A. Deluzarche, *C. R. Acad. Sci.* **223**, 1148 (1946).
- ⁵⁸¹ M. Colonna, *Boll. Sci. Fac. Chim. Ind. Univ. Bologna* **6**, 26 (1948); *Chem. Abstr.* **44**, 1985 (1950).
- ⁵⁸² M. DeClereq and N. P. Buu-Hoi, *C. R. Acad. Sci.* **227**, 1251 (1948).
- ⁵⁸³ M. DeClereq and N. P. Buu-Hoi, *C. R. Acad. Sci.* **227**, 1377 (1948).
- ⁵⁸⁴ A. M. El-Abbady, M. A. Omara, and N. G. Kandil, *Rev. Roum. Chim.* **18**, 899 (1973).
- ⁵⁸⁵ R. D. Garrett and H. R. Henze, *J. Med. Chem.* **9**, 976 (1966).
- ⁵⁸⁶ A. F. Isbell and H. R. Henze, *J. Amer. Chem. Soc.* **66**, 2096 (1944).
- ⁵⁸⁷ J. A. Knight, H. K. Porter, and P. K. Calaway, *J. Amer. Chem. Soc.* **66**, 1893 (1944).
- ⁵⁸⁸ L. C. March, W. A. Romanchick, G. S. Bajwa, and M. M. Joullie, *J. Med. Chem.* **16**, 337 (1973).
- ⁵⁸⁹ G. P. Mueller and R. E. Stobaugh, *J. Amer. Chem. Soc.* **72**, 1598 (1950).
- ⁵⁹⁰ Nguyen-Hoan and N. P. Buu-hoi, *C. R. Acad. Sci.* **224**, 1363 (1947).
- ⁵⁹¹ W. Ried and F. Kohlhaas, *Justus Liebigs Ann. Chem.* **707**, 242 (1967).
- ⁵⁹² W. Ried and P. Weidemann, *Chem. Ber.* **104**, 3341 (1971).
- ⁵⁹³ G. Stefanovic, L. Lorene, R. I. Mamuzie, and M. L. Mihailovic, *Tetrahedron* **6**, 304 (1958).
- ⁵⁹⁴ A. M. Dowell, H. S. McCullough, and P. K. Calaway, *J. Amer. Chem. Soc.* **70**, 226 (1948).
- ⁵⁹⁵ H. R. Henze, J. W. Melton, and E. O. Forman, *J. Amer. Chem. Soc.* **70**, 2622 (1948).
- ⁵⁹⁶ O. Nowell and P. K. Calaway, *J. Amer. Chem. Soc.* **69**, 116 (1947).
- ⁵⁹⁷ G. Stefanovic, M. Pavicic-woss, L. Lorene, and M. L. Mihailovic, *Tetrahedron* **6**, 97 (1959).



Cycloalkanones also react with isatin;^{27,32,207,471,552,557,567,573,599-612} for example, cyclohexanone and isatin gave **203**.⁶⁰⁹ Steroidal ketones have also been used.^{599,612a} Resorcinol and phloroglucinol appear to react analogously⁶¹³; resorcinol gave **204**.



Reaction of isatins with 3-chloro-2-butanone gave **205**.⁹ 1-(*o*-Tolyl)-isatins underwent a reaction similar to the Pfizinger synthesis to give **206**.⁷¹

Although aldehydes have not been used, oximes have been used to prepare 3-substituted quinoline-4-carboxylic acids.⁶¹⁴ The dioxime of

⁵⁹⁸ R. L. Sublett and P. K. Calaway, *J. Amer. Chem. Soc.* **70**, 674 (1948).

⁵⁹⁹ N. P. Buu-Hoi and P. Cagniant, *Ber.* **77**, 118 (1944).

⁶⁰⁰ N. P. Buu-Hoi, *J. Chem. Soc.*, 795 (1946).

⁶⁰¹ N. P. Buu-Hoi and P. Cagniant, *Bull. Soc. Chim. Fr.*, 343 (1944).

⁶⁰² N. P. Buu-Hoi and R. Royer, *Rec. Trav. Chim.* **66**, 300 (1947).

⁶⁰³ P. Cagniant and A. Deluzarche, *C.R. Acad. Sci.* **223**, 808 (1946).

⁶⁰⁴ J. Colonge and J. Chambion, *C.R. Acad. Sci.* **224**, 128 (1947).

⁶⁰⁵ P. Jacquignon and N. P. Buu-Hoi, *J. Org. Chem.* **22**, 72 (1957).

⁶⁰⁶ L. E. Kholodov, G. P. Syrova, V. G. Yashunskii, and Y. N. Sheinker, *Khim. Geterotsikl. Soedin.*, 78 (1970).

⁶⁰⁷ R. Madhav and P. L. Southwick, *J. Heterocycl. Chem.* **9**, 443 (1972).

⁶⁰⁸ F. G. Mann, *Nature (London)* **164**, 785 (1949).

⁶⁰⁹ E. A. Markaryan and R. S. Balayan, *Sin. Geterotsikl. Soedin.*, 74 (1972); *Chem. Abstr.* **79**, 146357 (1973).

⁶¹⁰ N. P. Buu-Hoi and R. Royer, *C.R. Acad. Sci.* **223**, 806 (1946).

⁶¹¹ G. A. Klimov, V. A. Stonik, and M. N. Tilichenko, *Khim. Geterotsikl. Soedin.*, 821 (1973).

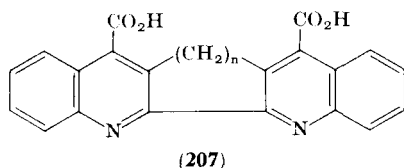
⁶¹² I. F. Tishchenkova, L. E. Kholodov, and V. G. Yashunski, *Khim. Geterotsikl. Soedin.* **7**, 102 (1971).

^{612a} A. Hassner and M. J. Haddadin, *J. Org. Chem.* **27**, 1911 (1962).

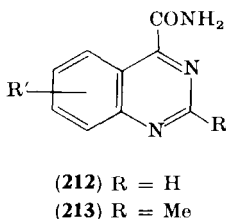
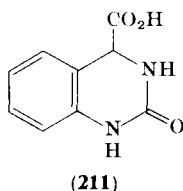
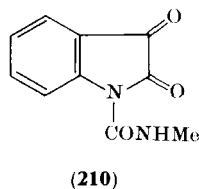
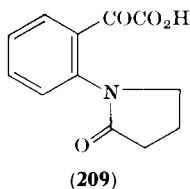
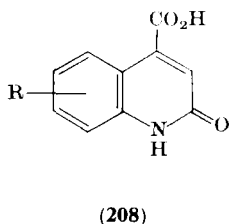
⁶¹³ W. H. Linnell and L. K. Sharp, *Quart. J. Pharm. Pharmacol.* **21**, 58 (1948).

⁶¹⁴ M. Haring and G. Stille, *Helv. Chim. Acta* **44**, 642 (1961).

1,2-cyclopentanedione and 1,2-cyclohexanedione undergo a modified Pfitzinger reaction to give **207**.⁶¹⁵



Treatment of *N*-acetylisisatin with base gave the quinolone **208**,^{16,32,616-620a} while *N*-propionylisatin gave the 3-methyl analog of



208,¹⁶⁸ and isatin with *p*-nitrophenylacetic anhydride gave the 3-(*p*-nitrophenyl) analog of **208**.^{620b} The use of 1-(chloroacetyl)isatin in this reaction has also been studied;^{163,459,621} it gives 2,4-dioxoquinoline and 3-hydroxy-2-quinolone. *N*-(4-Chlorobutyl)isatin gave **209** in an abnormal example of this reaction.¹⁵⁸ Use of **210** gave **211**.¹²³ Compounds similar to **211** have been obtained from isatin and allylisothiocyanates in the presence of base.⁶²² Quinazolines **212** and **213** are also

⁶¹⁵ E. Uhlemann and P. Kurze, *J. Prakt. Chem.* **312**, 1105 (1970).

⁶¹⁶ J. Buchi, H. Hurni, and R. Lieberherr, *Helv. Chim. Acta* **32**, 1806 (1949).

⁶¹⁷ J. Buchi and X. Perlia, *Arzneimittel-Forsch.* **10**, 174 (1960).

⁶¹⁸ R. A. Egli and C. Richter, *Helv. Chim. Acta* **40**, 499 (1957).

⁶¹⁹ K. Ohata, H. Fukumi, K. Kobayashi, H. Matsushima, and M. Koremura, Japan Patent 72 16,477 (1972); *Chem. Abstr.* **77**, 164523 (1972).

⁶²⁰ C. R. Wetzell, J. R. Shanklin, and R. E. Lutz, *J. Med. Chem.* **16**, 528 (1973).

^{620a} H. Fukumi, K. Oohata, M. Matsushima, and K. Arima, *J. Pharm. Soc. Japan* **94**, 768 (1974).

^{620b} S. Yoshima and A. Tanaka, *J. Pharm. Soc. Japan* **94**, 267 (1974).

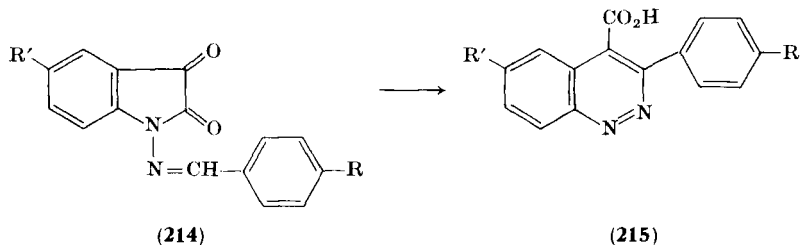
⁶²¹ J. R. Price and L. W. Smith, *Aust. J. Chem.* **9**, 139 (1956).

⁶²² G. M. Sharma, K. K. Soni, and K. S. Narang, *Tetrahedron* **18**, 1019 (1962).

obtained from *N*-formyl and *N*-acetyl isatin by treatment with sodium hydroxide and then ammonia.⁹⁸

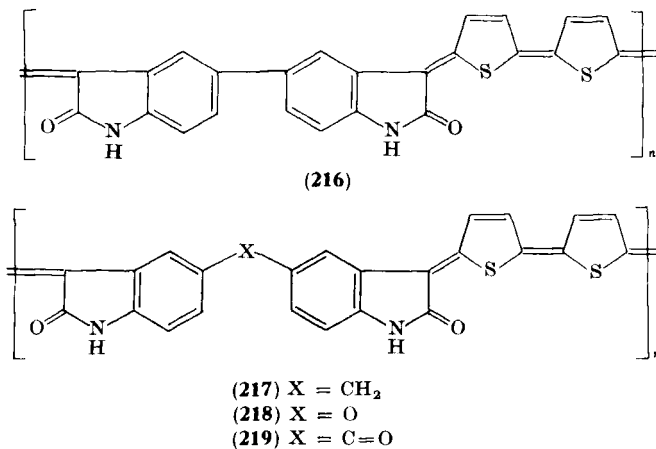
Pyruvic acid and isatins gave quinoline-2,4-dicarboxylic acids.^{16,36} Use of malonic acid with isatins gave 2-quinolone-4-carboxylic acids.^{169,620} Nitromethane and isatin with 50% potassium hydroxide gave 3-nitroquinoline-4-carboxylic acid.⁶²³

A number of cinnolines have been obtained by alkali treatment of isatins. Thus, **214** gave **215**,⁶⁸⁻⁷⁰ while isatin on treatment with base followed by hydrogen and palladium, diazotization, and reduction gave 3-hydroxycinnoline.⁶²⁴



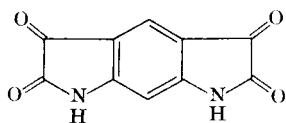
XI. Polymers

5,5'-Biisatin, 5,5'-methylenebiisatin, 5,5'-diisatylether, and 5,5'-diisatylketones have proved to be useful compounds for the preparation of polymers. A series of polyindophenines (**216-219**) have been prepared by reaction of these isatins with thiophene under acidic condi-

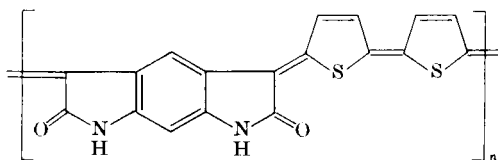


⁶²³ M. Colonna, *Boll. Sci. Fac. Chim. Ind. Bologna*, 89 (1941); *Chem. Abstr.* **37**, 3096 (1943).

⁶²⁴ R. L. Zey, *J. Heterocycl. Chem.* **9**, 1177 (1972).



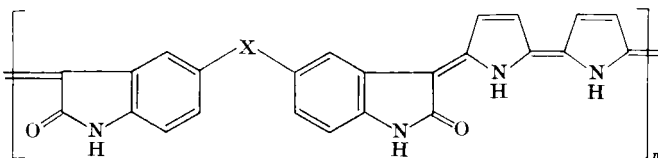
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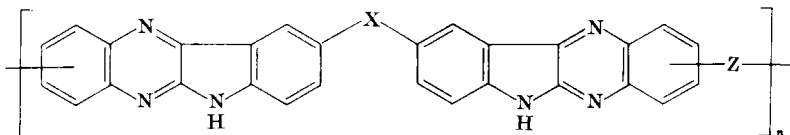
(221)

tions.^{59,544,625-628} Polyphosphoric acid is very effective for this polymerization.^{59,544,627,628} These vat polymers can be reduced to the leuco form,^{59,625,626,628} and their semiconductor properties have been discussed.^{544,629} Sulfuric acid-catalyzed copolymerization of **220** and thiophene gave the polymeric vat dye **221**.⁶³⁰

In a manner similar to that noted above, pyrrole gave polypyrrole-indophenines (**222**, X = O, CH₂, and a bond),⁶³¹ and *o*-diamines gave polyindoloquinoxalines **223**,⁴²⁴ **224**,^{424,632} **225**,⁶³³ **226**,⁴²³ **227**,⁴²³ and **228**.⁴²³ These latter compounds showed good thermal stability. Polymer



(222)



(223) X = bond, Z = bond

(224) X = O, Z = O

(225) X = O, Z = CH₂

(226) X = CH₂, Z = bond

(227) X = CH₂, Z = CH₂

(228) X = CH₂, Z = O

⁶²⁵ I. J. Levine, U.S. Patent 3,334,074 (1967); *Chem. Abstr.* **67**, 82565 (1967).

⁶²⁶ I. Shopov, *Polymer Lett.* **4**, 1023 (1966).

⁶²⁷ I. Shopov, *C.R. Acad. Bulg. Sci.* **21**, 439 (1968).

⁶²⁸ I. Shopov and K. Vodenicharov, *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk* **3**, 445 (1970).

⁶²⁹ I. Shopov and K. Vodenicharov, *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk* **3**, 233 (1970).

⁶³⁰ G. Kossmehl and G. Manecke, *Makromol. Chem.* **113**, 182 (1968).

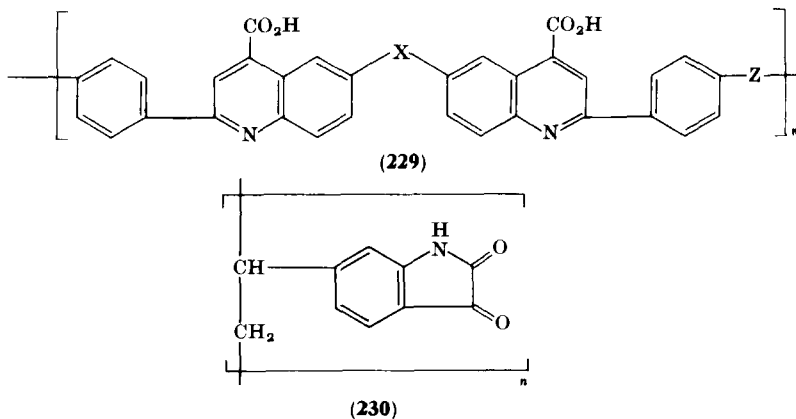
⁶³¹ I. Shopov, N. Kassabova, and M. Vodenicharova, *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk* **4**, 629 (1971).

⁶³² I. Shopov and N. Popov, *Vysokomol. Soedin., Ser. B* **9**, 415 (1967); *Chem. Abstr.* **67**, 82457 (1967).

⁶³³ M. Kurihara and N. Yoda, Japan Patent 70 40,552 (1970); *Chem. Abstr.* **74**, 126522 (1971).

225 was prepared at 150–250° rather than in the presence of polyphosphoric acid. The EPR spectra of several of the polyindoloquinoxalines have been reported.⁶³⁴

Polyphenylenequinolines (**229**) have been prepared through a Pfitzinger type reaction.⁵⁶⁹ Use of acetylated polystyrene with isatin in



the Pfitzinger reaction gave a cinchoninic acid derivative of polystyrene.⁶³⁵ The Sandmeyer isonitrosoacetanilide isatin synthesis has been applied to poly(*m*-aminostyrene) to give poly(6-vinylisatin) (**230**).^{636,637} Polymer **230** has been converted into poly(6-vinylindirubine) and poly[(6-vinyl-3-indole)(2-thionaphthene)]indigo, and all three polymers were investigated with regard to their redox capacity and standard redox potential.^{636,637}

Note Added in Proof: Since the completion of this review the following additional reports have appeared.

Section III: H. Boehme and H. Schwartz, *Arch. Pharm.* **307**, 775 (1974); M. Furukawa, T. Suda, and S. Hayashi, *Chem. Lett.*, 881 (1974).

Section VII: Y. S. Chough and K. I. Kang, *Yakhak Hoeji* **17**, 141 (1973); *Chem. Abstr.* **81**, 151896 (1974); R. S. Pandit and S. Seshadri, *Indian J. Chem.* **12**, 943 (1974); A. B. Tomchin and E. A. Rusakov, *Khim.-Farm. Zg.* **8**, 23 (1974).

Section VIII: V. M. Dziomko, A. V. Ivashchenko, and R. V. Poponova, *Zh. Org. Khim.* **10**, 1325 (1974); M. Furukawa, T. Yoshida, and S. Hayashi, *Chem. Pharm. Bull.* **22**, 2875 (1974); M. Seth, A. P. Bhaduri, N. M. Khanna, and M. L. Dhar, *Indian J. Chem.* **12**, 124 (1974).

Section IX: B. Lal, P. Singh, and A. P. Bhaduri, *Indian J. Chem.* **12**, 906 (1974); G. I. Zhungietu and L. M. Reulets, *Khim. Geterotsikl. Soedin.*, 1226 (1974).

Section X: S. Petersen, Germ. Patent 2,314,242 (1974); *Chem. Abstr.* **82**, 4296 (1975).

⁶³⁴ I. Shopov and N. Iordanov, *Dokl. Bolg. Akad. Nauk* **22**, 1123 (1969); *Chem. Abstr.* **72**, 56038 (1970).

⁶³⁵ J. A. Blanchette, U.S. Patent 2,865,902 (1958); *Chem. Abstr.* **53**, 7668 (1959).

⁶³⁶ G. Kossmehl and G. Manecke, *Makromol. Chem.* **115**, 285 (1968).

⁶³⁷ G. Manecke and G. Kossmehl, *Makromol. Chem.* **70**, 112 (1964).

Thiochromanones and Related Compounds

S. W. SCHNELLER

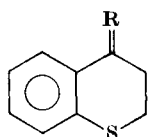
*Department of Chemistry, University of South Florida,
Tampa, Florida*

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I. Introduction

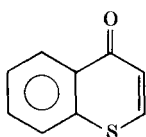
The scarcity of reviews¹ and recent interest in thiochromanones and related compounds calls for a comprehensive summary of this area of heterocyclic chemistry. The apparent similarity between these systems and the naturally occurring chromanones, chromones (flavones), chromenes, etc., is responsible for the continued importance of these sulfur heterocycles. *Chemical Abstracts* (through November, 1973) has been employed as the principal reference source and nomenclature guide for this review.

The focus will be directed to five ring systems: thiochromans (1), thiochromones (2), isothiochromans (3), benzothiopyrans (4-6), and benzothiopyrylium salts (7, 8). It is difficult completely to segregate their chemistry since they are so interrelated; cross-references will be employed as often as possible. Thiocoumarins and thioxanthenes are excluded since these molecules differ considerably from those reviewed here.



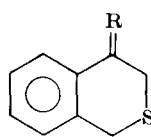
(1)

Thiochromans
R = H₂; H, OH
Thiochromanones
R = O



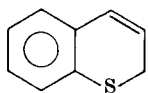
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Thiochromones



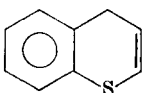
(3)

Isothiochromans
R = H₂; H, OH
Isothiochromanones
R = O



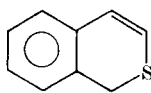
(4)

2H-1-Benzothiopyrans



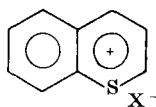
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4H-1-Benzothiopyrans



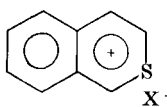
(6)

1H-2-Benzothiopyrans



(7)

1-Benzothiopyrylium salts



(8)

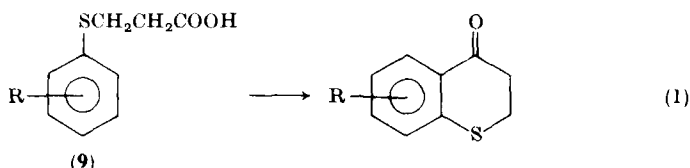
2-Benzothiopyrylium salts

¹ D. S. Tarbell, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 2, Chapter 14. Wiley, New York, 1951.

II. Thiochromans and Thiochroman-4-ones

A. PREPARATION OF THIOCHROMAN-4-ONES

Thiochroman-4-ones (**1**; R = O) have been the most convenient synthetic entry into the thiochroman ring system. The most profitable of the various routes has been the acid-promoted cyclodehydration of β -arylmercaptopropionic acids (**9**) [Eq. (1)]. The acids (**9**) result from



nucleophilic displacement of a thiophenoxide on a β -halopropionic acid²⁻⁶ or ester⁷ or nucleophilic ring opening of a β -propiolactone⁸⁻¹⁰ with alkyl oxygen cleavage. Sulfuric acid,^{2,3,6,7,10} polyphosphoric acid,^{5,11-13} phosphorus pentoxide,^{5,9} hydrogen fluoride,¹⁴ and several Lewis acids¹⁵ catalyze the cyclization of (9). Various substituted thiophenols and propionic acids or propiolactones may be used. Lewis acid¹⁵ catalysts frequently circumvent side reactions unavoidable with mineral acids [cf. Eq. (2)]. Lewis acids also cyclize the corresponding β -arylmercaptopropionyl halides to derivatives of **1** (R = O).¹⁶

² C. Finzi, *Gazz. Chim. Ital.* **56**, 539 (1926).

³ V. Bellavita, *Gazz. Chim. Ital.* **62**, 655 (1932).

⁴ V. Bellavita, *Gazz. Chim. Ital.* **70**, 594 (1940).

⁵ N. Cagnoli, A. Ricci, and N. Fedi, *Ann. Chim. (Rome)* **47**, 606 (1957); *Chem. Abstr.* **51**, 16454 (1957).

⁶ I. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna* **24**, 75 (1966); *Chem. Abstr.* **66**, 46292 (1967).

⁷ F. Krollpfeiffer and H. Schultze, *Ber.* **56B**, 1919 (1923).

⁸ H. E. Zaugg, H. J. Glenn, R. J. Michaels, R. V. Shock, and L. R. Swett, *J. Amer. Chem. Soc.* **79**, 3912 (1957).

⁹ A. B. Sen and S. L. Arora, *J. Indian Chem. Soc.* **35**, 197 (1958).

¹⁰ H. E. Zaugg, R. J. Michaels, and H. J. Glenn, U.S. Patent 2,940,992; *Chem. Abstr.* **54**, 20990 (1960).

¹¹ C. D. Hurd and Shin Hayao, *J. Amer. Chem. Soc.* **76**, 5065 (1954).

¹² G. Kunesch and F. Wessely, *Monatsh. Chem.* **96**, 1547 (1965).

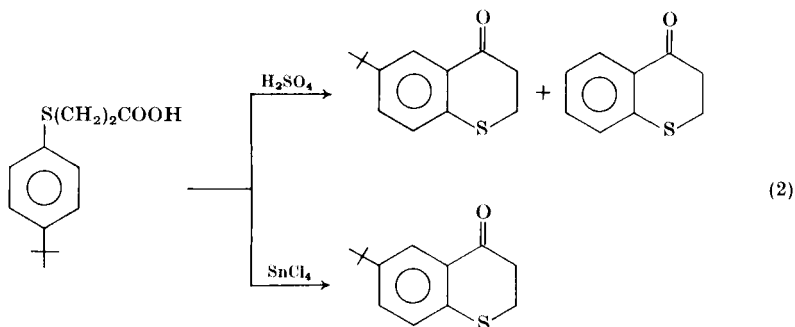
¹³ N. Cagnoli, A. Martani, and C. Rossi, *Ann. Chim. (Rome)* **56**, 1075 (1966); *Chem. Abstr.* **66**, 55338 (1967).

¹⁴ D. S. Tarbell, H. P. Hirschler, and T. J. Hall, *J. Amer. Chem. Soc.* **75**, 1985 (1953).

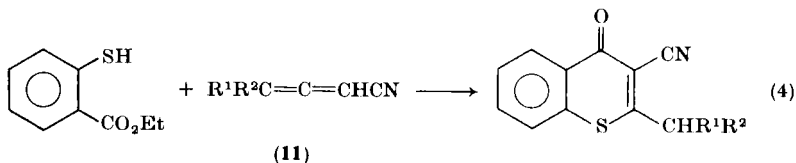
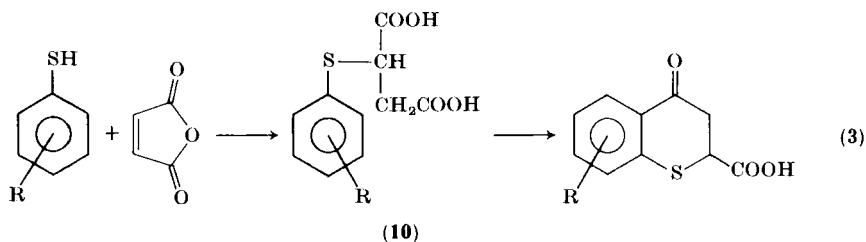
¹⁵ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.* 3674 (1966).

¹⁶ W. E. Truce and J. P. Milonis, *J. Amer. Chem. Soc.* **74**, 974 (1952).

Compound 9 has also been obtained via nucleophilic displacements by thioglycolic acids on activated halobenzenes^{12,13} and Michael addition to acrylate esters^{14,17,18} or acrylonitriles¹⁹ with subsequent hydrolysis.



Further synthetic entries into the thiochromanone ring system have involved arylmercaptosuccinic acids^{20,21} (**10**) as in Eq. (3) and the reaction of ethyl *o*-mercaptobenzoates with 2,3-diene carbonitriles²² as in Eq. (4). 3-Substituted thiochromanones (**12**) are prepared by the



¹⁷ J. C. Petropoulos, M. A. McCall, and D. S. Tarbell, *J. Amer. Chem. Soc.* **75**, 1130 (1953).

¹⁸ F. Arndt, L. Loewe, and E. Ayca, *Chem. Ber.* **84**, 329 (1951).

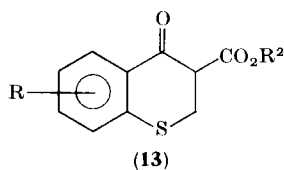
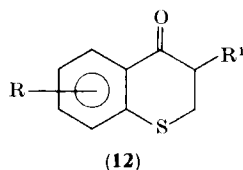
¹⁹ A. P. Momsenko, *Zh. Org. Khim.* **9**, 775 (1973); *Chem. Abstr.* **79**, 31797 (1973).

²⁰ J. Schmutz, H. Lavener, R. Hirt, and M. Lanz, *Helv. Chim. Acta* **34**, 767 (1951).

²¹ E. W. Bousquet, U.S. Patent 2,434,100; *Chem. Abstr.* **42**, 2289 (1948).

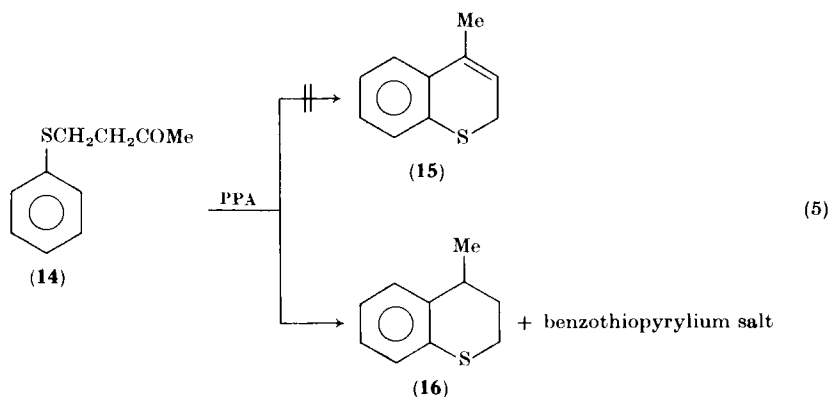
²² I. T. Kay and N. Punja, *J. Chem. Soc. C* **2409** (1970).

alkylation of 3-carbalkoxythiochroman-4-ones (**13**) with subsequent saponification and decarboxylation.²³



B. PREPARATION OF THIOCHROMANS

Thiochromans (**1**; R = H₂) result from disproportionation of 2*H*-1-benzothiopyrans (**4**) and also from thio-Claisen rearrangements of phenyl allyl sulfides. The first pathway was discovered by Tilak and Vaidya,²⁴ who attempted to prepare one benzothiopyran (**15**) by cyclizing the β -ketosulfide (**14**) in polyphosphoric acid (PPA), but obtained the thiochroman (**16**) and a benzothiopyrylium salt as in Eq. (5). This reaction involves^{25,26} an acid-promoted disproportionation



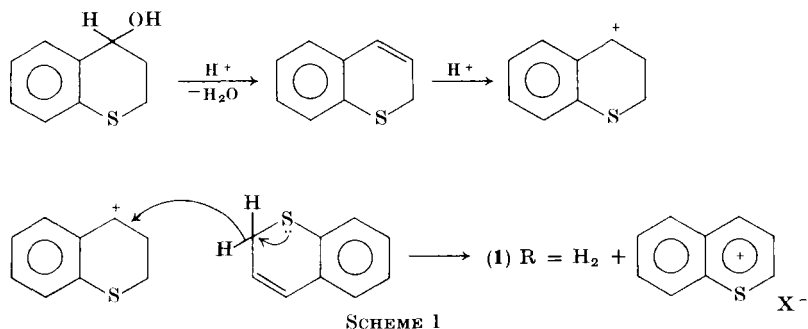
via a hydride transfer in **15** (cf. Scheme 1), which was expanded to a variety of thiochromans and thiocyanine dyes (from the benzothiopyrylium salts accompanying formation of **1**, R = H₂).

²³ J. R. Boissier and C. Malen, French Patent 1,367,604; *Chem. Abstr.* **61**, 14642 (1964).

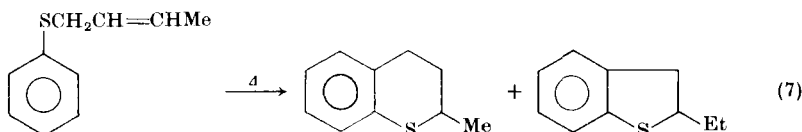
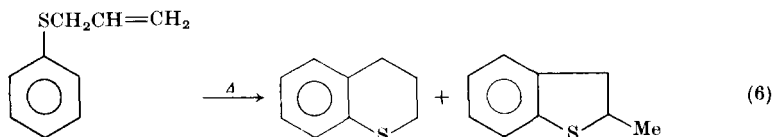
²⁴ B. D. Tilak and V. M. Vaidya, *Tetrahedron Lett.*, 487 (1963).

²⁵ B. D. Tilak, R. B. Mitra, and V. D. Chandrakala, *Tetrahedron Lett.*, 3569 (1965).

²⁶ B. D. Tilak, H. S. Desai, C. V. Deshpande, S. K. Jain, and V. M. Vaidya, *Tetrahedron* **22**, 7 (1966).



Thiochroman (**1**; R = H₂) is a product of the thio-Claisen rearrangement of allyl phenyl sulfide, as reported in 1963;²⁷ this reaction also produces 2,3-dihydrothiophenes as shown in Eqs. (6) and (7).^{28,29}



Similar reactions were carried out on **17**,²⁹ **18**,³⁰ and **19**.³⁰ The last gave thiochromans and 2,3-dihydrothiophenes from an apparent cyclization at the ortho methyl substituent, but in fact involving a variety of hydrogen and methyl shifts. The route to the two main products [Eq. (7)] of the thio-Claisen rearrangement has been suggested to be via the thiirane intermediate (**20**).³¹

This rearrangement is also catalyzed by Lewis acids,³² but the products are more varied and this method is, therefore, less advantageous as a synthesis of thiochromans.

²⁷ C. Y. Meyers, C. Rinaldi, and L. Bonoli, *J. Org. Chem.* **28**, 2440 (1963).

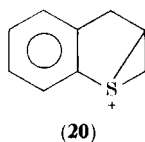
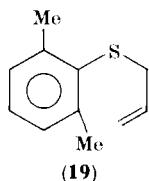
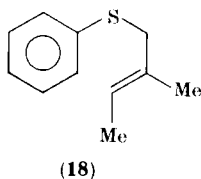
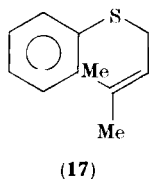
²⁸ T. A. Danilova, T. Abdin, and E. A. Viktorova, *Neftekhimiya* **11**, 444 (1971); *Chem. Abstr.* **75**, 76324 (1971).

²⁹ J. Tanaka, T. Katagiri, K. Takabe, and S. Takeshita, *Yuki Gosei Kagaku Kyokai Shi* **29**, 788 (1971); *Chem. Abstr.* **75** 140636 (1971).

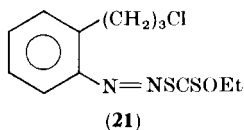
³⁰ H. Kwart and M. H. Cohen, *Chem. Commun.*, 1296 (1968).

³¹ H. Kwart and E. R. Evans, *J. Org. Chem.* **31**, 413 (1966).

³² S. Khushvakhitova, E. A. Viktorova, and T. A. Danilova, *Vestn. Mosk. Univ., Khim.* **24**, 99 (1969); *Chem. Abstr.* **72**, 12260 (1970).



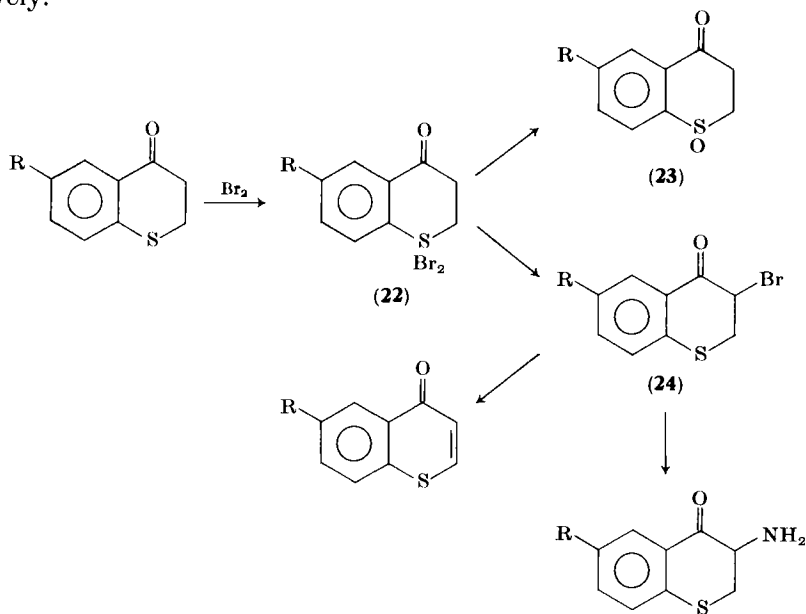
Thiochromans and thiochroman 1,1-dioxides are readily prepared³³⁻³⁵ from the corresponding thiochroman-4-one by catalytic hydrogenation in acetic acid/perchloric acid or via the Wolff-Kishner and Clemensen^{6,17} methods. Thermal decomposition of **21** produced thiochroman in 85% yield.³⁶ Thiochroman and isothiochroman occur in petroleum,³⁷ and the completely saturated analog of the former (1-thiadecalin) was obtained³⁸⁻⁴² from propenyl 1-cyclohexenyl ketones in the presence of hydrogen sulfide and sodium acetate in ethanol.



- ³³ J. R. Boissier and R. Ratorius, French Patent 1,574,139; *Chem. Abstr.* **72**, 100522 (1970).
- ³⁴ S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol., London* **40**, 76 (1954); *Chem. Abstr.* **49**, 8243 (1955).
- ³⁵ J. B. Campbell, E. R. Lavagino, R. B. Morin, and D. O. Spry, *Ann. N.Y. Acad. Sci.* **172**, 261 (1970).
- ³⁶ J. v. Braun, *Ber.* **43**, 3220 (1910).
- ³⁷ S. F. Birch, *J. Inst. Petrol., London* **39**, 185 (1953); *Chem. Abstr.* **47**, 10211 (1953).
- ³⁸ E. N. Karaulova, V. Sh. Shaikhrazieva, and G. D. Gal'pern, *Khim. Geterotsikl. Soedin.*, 51 (1967); *Chem. Abstr.* **67**, 64185 (1967).
- ³⁹ V. Sh. Shaikhrazieva, E. N. Karaulova, G. D. Gal'pern, D. K. Zhestkov, and I. V. Cherepanova, *Khim. Seraorg. Soedin., Soderzh. Neftyakh Neftprod.* **8**, 95 (1968); *Chem. Abstr.* **71**, 91222 (1969).
- ⁴⁰ V. I. Dronov, V. P. Krivonogov, and V. S. Nikitina, *Khim. Geterotsikl. Soedin.*, 335 (1970); *Chem. Abstr.* **73**, 66363 (1970).
- ⁴¹ V. I. Dronov and V. P. Krivonogov, USSR Patent 281,459; *Chem. Abstr.* **74**, 87507 (1971).
- ⁴² V. G. Kharchenko, N. M. Kupranets, M. E. Stankevich, and M. N. Berezhnaya, USSR Patent 287,028; *Chem. Abstr.* **75**, 35745 (1971).

C. REACTIONS OF THIOCHROMAN-4-ONES

Halogenation of thiochromanones is a fruitful entry into other systems. As shown in Scheme 2, bromination of 6-methylthiochroman-4-one produces the perbromide (**22**), converted by water into the sulfoxide (**23**). Upon standing, **22** loses hydrogen bromide to form the 3-bromo compound (**24**), which yields the 3-amino analog and 6-methylthiochrom-4-one with ammonia and dimethylaniline, respectively.^{43,44}



SCHEME 2

3-Bromothiochroman-4-ones are generally ring opened by hydroxide to thiosalicylic acids,⁴⁵ with formaldehyde they yield the corresponding 3-epoxy system (**25**) which can be converted into the 3-hydroxymethyl isomer (**26**).⁴⁶ Attempts to convert **25** into benzothiepins via acid-mediated ring expansions have failed, yielding thiochromanones instead.^{47,48}

⁴³ F. Krollpfeiffer, H. Schultze, E. Schlumbohm, and E. Sommermeyer, *Ber.* **58B**, 1654 (1925).

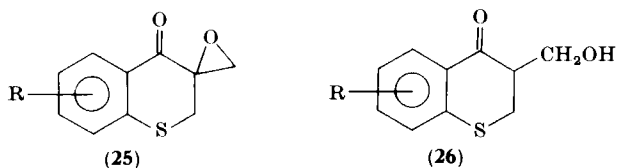
⁴⁴ W. Baker, *J. Chem. Soc.* **127**, 2349 (1925).

⁴⁵ F. Krollpfeiffer, H. Schultze, and E. Sommermeyer, *Ber.* **58B**, 2698 (1925).

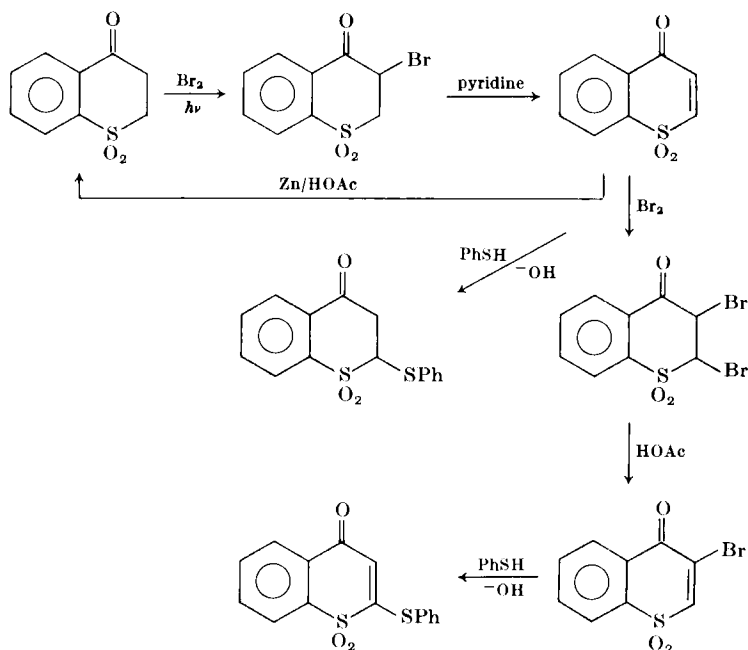
⁴⁶ H. Hofmann, G. Salbeck, and B. Meyer, *Chem. Ber.* **103**, 2084 (1970).

⁴⁷ H. Hofmann, H. Westnacher, and H. J. Haberstroh, *Chem. Ber.* **106**, 349 (1973).

⁴⁸ H. Hofmann and H. Westnacher, *Chem. Ber.* **102**, 205 (1969).



Scheme 3 demonstrates similar reactions for thiochroman-4-one 1,1-dioxide (available from hydrogen peroxide oxidation of thiochroman 4-one).⁴⁹



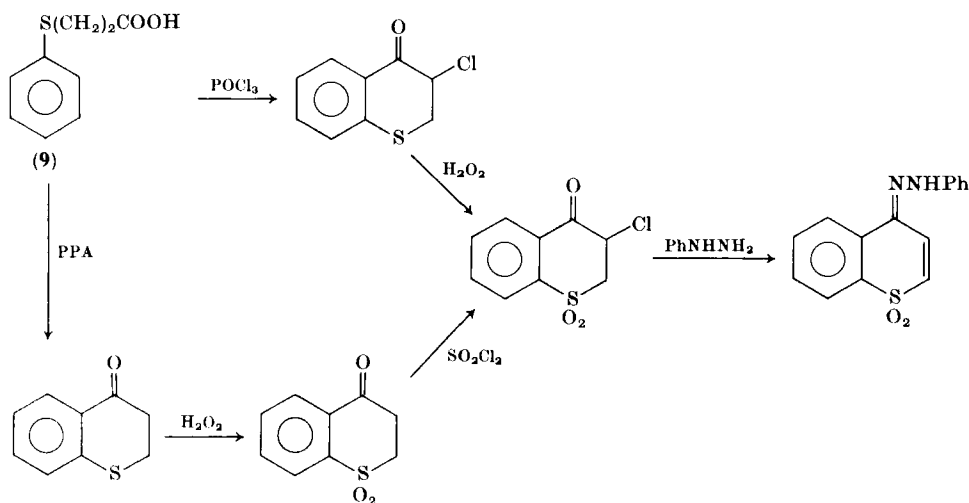
SCHEME 3

Chlorination¹¹ of thiochroman-4-one is best achieved by cyclizing the requisite β -arylmercaptopropionic acid (9) with phosphorus oxychloride. Conversions related to this are presented in Scheme 4.

Thiochroman-4-ones are reduced to thiochroman-4-ols by sodium borohydride⁶ and lithium aluminum hydride.⁵⁰ Lithium aluminum hydride reduction of thioflavan-4-ones (27) forms the 2,4-*cis*-thioflavan-4-ols (28) as in Eq. (8). By contrast, deamination of 2,4-*cis*-4-aminothioflavans (29) with nitrous acid produced the *trans*-alcohol (30) as shown in Eq. (9).⁵⁰ The alcohols obtained by the hydride reductions have

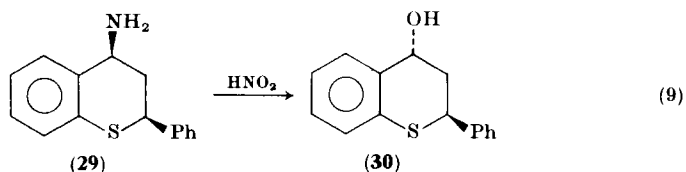
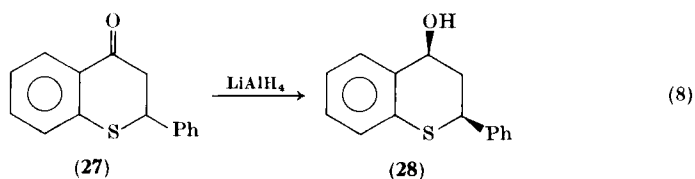
⁴⁹ T. Nambara, *Yakugaku Zasshi* **78**, 624 (1958); *Chem. Abstr.* **52**, 18392 (1958).

⁵⁰ G. F. Katekar, *Aust. J. Chem.* **19**, 1251 (1966).



SCHEME 4

frequently been employed for the preparation of 1-benzothiopyrylium salts by dehydration (potassium hydrogen sulfate, phosphorus pentoxide, etc.) to 2H-1-benzothiopyran (4) and subsequent hydride loss.^{6,51,52} (e.g., Section VI,A)



As mentioned (Section II, B), thiochroman-4-ones are readily reduced to the methylene level catalytically,³³⁻³⁵ under Clemmensen conditions,^{16,17} and, occasionally, with lithium aluminum hydride.⁵³ The

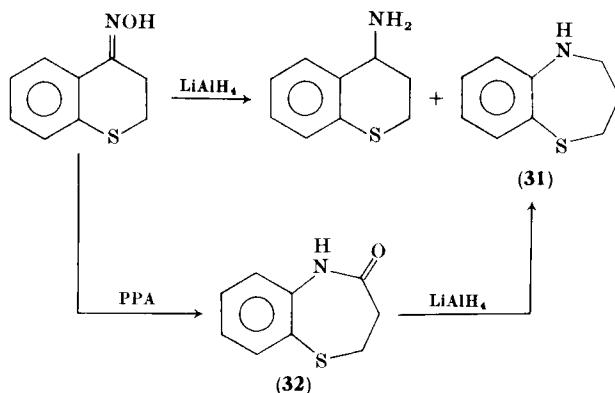
⁵¹ A. Lüttringhaus and N. Englehard, *Naturwissenschaften* **44**, 584 (1957).

⁵² W. Bonthrone and D. H. Reid, *Chem. Ind. (London)*, 1192 (1960).

⁵³ C. Angelini, G. Grandolini, and L. Mignini, *Ann. Chim. (Rome)* **46**, 235 (1956); *Chem. Abstr.* **51**, 396 (1957).

ketone moiety of **1** ($R = O$) undergoes other typical reactions such as the formation of thiochroman-4-ols with organometallic reagents,¹⁷ (e.g., Grignard, organolithium) and oximes and hydrazones with hydroxylamine and various hydrazines, respectively.

The 4-oximes are convenient intermediates. Reduction with zinc/acetic acid,⁵⁴ hydrogen over palladium on charcoal^{55,56} or nickel,⁵⁷ or lithium aluminum hydride,⁵⁵ produces the 4-aminothiochroman. Interestingly, lithium aluminum hydride induces ring expansion to the



SCHEME 5

2,3,4,5-tetrahydro-1,5-benzothiazepine (**31**), usually isolated as the *p*-toluenesulfonyl derivative⁵⁸⁻⁶¹ (Scheme 5). Compound **31** also results from the Beckmann rearrangement of the oxime to **32** and subsequent lithium aluminum hydride reduction (Scheme 5).⁵⁸⁻⁶⁰ The

⁵⁴ G. M. Bennett and W. B. Waddington, *J. Chem. Soc.*, 1692 (1931).

⁵⁵ R. Bognar, M. Rakosi, and J. Balint, *Tetrahedron Lett.*, 137 (1964).

⁵⁶ R. Bognar and M. Rakosi, *Justus Liebigs Ann. Chem.* **693**, 225 (1966).

⁵⁷ N. V. Dudykina and V. A. Zagorevskii, *Sin. Prir. Soedin., Ikh Analog. Fragmentov, Akad. Nauk SSSR, Otd. Obshch. Tekhn. Khim.*, 139 (1965); *Chem. Abstr.* **65**, 8866 (1966).

⁵⁸ V. A. Zagorevskii and N. V. Dudykina, *Zh. Obshch. Khim.* **33**, 322 (1963); *Chem. Abstr.* **59**, 631 (1963).

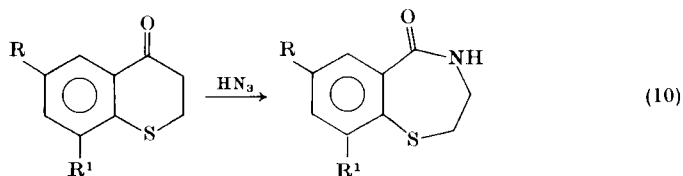
⁵⁹ V. A. Zagorevskii and N. V. Dudykina, *Zh. Obshch. Khim.* **34**, 2282 (1964); *Chem. Abstr.* **61**, 11960 (1964).

⁶⁰ N. V. Dudykina and V. A. Zagorevskii, *Sin. Prior. Soedin. Ikh. Analog. Fragmentov, Akad. Nauk SSSR, Otd. Obshch. Tekhn. Khim.*, 134 (1965); *Chem. Abstr.* **65**, 683 (1966).

⁶¹ V. A. Zagorevskii, N. V. Dudykina, and L. M. Mescheryakova, *Zh. Org. Khim.* **5**, 1709 (1969); *Chem. Abstr.* **72**, 3316 (1970).

Neber reaction produces the corresponding 3-aminothiochroman-4-one.⁶² Similar reactions have been conducted on the *S,S*-dioxide oxime analogs.⁶³

Ring expansion of thiochroman-4-ones to 5-oxo-2,3,4,5-tetrahydro-1,4-benzothiazepines is accomplished by the Schmidt reaction, cf. Eq. (10).⁶⁴



Hydrazones of thiochroman-4-ones are converted into thiochromans under Wolff-Kishner-Huang conditions⁶⁵ and into the azo dimers by silver oxide.⁶⁶ Fisher indolization of the phenylhydrazones (33) gives 6,11-dihydrobenz[b]indolo[2,3-*d*]thiopyrans (34), which by hydride loss form the thiopyrylium salts (35), or on dehydrogenation produce the pseudoazulenes (36) (heterocyclic analogs of the carcinogen, benz[*a*]-carbazole), as shown in Scheme 6.⁶⁷⁻⁷³

Thiochroman-4-one reacts with isatin in the presence of potassium hydroxide to form benzothiopyrano[4,3-*b*]quinoline-7-carboxylic acids as illustrated in Eq. (11).^{67,74,75} The carbethoxyhydrazone (37) is

⁶² V. Dudykina and V. A. Zagorevskii, *Zh. Org. Khim.* **2**, 2222 (1966); *Chem. Abstr.* **66**, 75878 (1967).

⁶³ W. E. Truce and J. A. Simms, *J. Org. Chem.* **22**, 617 (1957).

⁶⁴ K. H. Wuensch, K. H. Stahnke, and A. Ehlers, *Chem. Ber.* **103**, 2302 (1970).

⁶⁵ N. Bellinger, D. Cagniant, and P. Cagniant, *Tetrahedron Lett.*, **49** (1971).

⁶⁶ F. Klages, M. Thuemmler, and M. Hoedl, *Chem. Ber.* **101**, 2153 (1968).

⁶⁷ F. G. Mann and B. B. Smith, *J. Chem. Soc.*, 1898 (1951).

⁶⁸ L. A. Aksanova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.* **33**, 220 (1963); *Chem. Abstr.* **59**, 2783 (1963).

⁶⁹ N. F. Kucherova, L. A. Aksanova, and V. A. Zagorevskii, *Zh. Obshch. Khim.* **33**, 3403 (1963); *Chem. Abstr.* **60**, 5471 (1964).

⁷⁰ A. Fravolini and A. Martani, *Boll. Sci. Fac. Chim. Ind. Bologna* **26**, 227 (1968); *Chem. Abstr.* **70**, 106414 (1969).

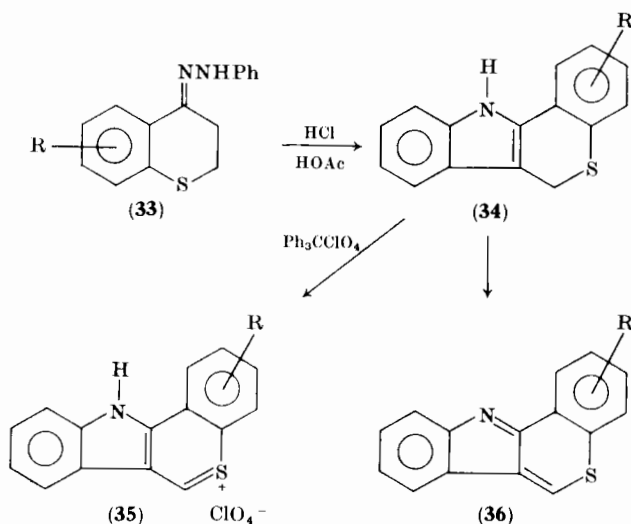
⁷¹ T. E. Young and P. H. Scott, *J. Org. Chem.* **30**, 3613 (1965).

⁷² N. P. Buu-Hoi, A. Martani, A. Croisy, P. Jacquignon, and F. Perin, *J. Chem. Soc. C*, 1787 (1966).

⁷³ T. E. Young and P. H. Scott, U.S. Patent 3,388,133; *Chem. Abstr.* **69**, 59213 (1968).

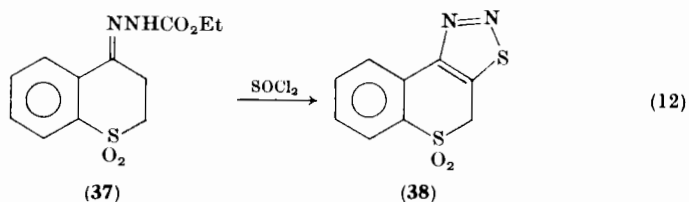
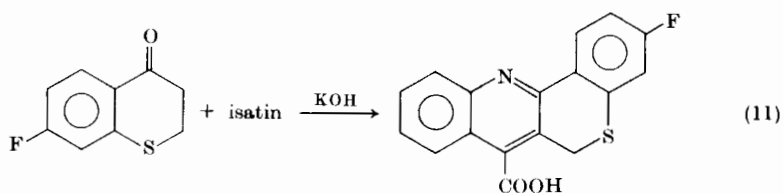
⁷⁴ P. Cagniant and A. Deluzarche, *C.R. Acad. Sci.*, **223**, 808 (1946).

⁷⁵ A. Fravolini and C. Rodriguez Salazar, *Ann. Chim. (Rome)* **58**, 1155 (1968); *Chem. Abstr.* **70**, 47334 (1969).



SCHEME 6

converted into 4*H*-[1,2,3]thiadiazolo[5,4-*c*]benzothiopyran 5,5-dioxides (38) with thionyl chloride⁷⁶ as shown in Eq. (12).



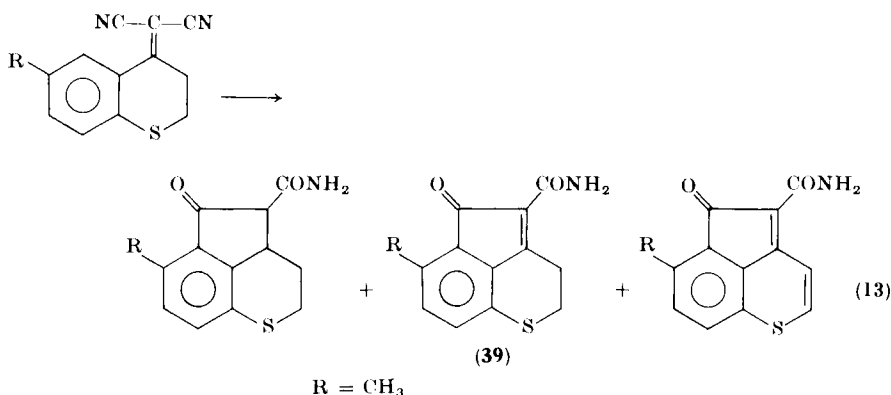
3-Methoxymethylene thiochroman-4-one⁷⁷ with formamidine forms 5*H*-1-benzothiopyrano[4,3-*d*]pyrimidine, with *o*-phenylenediamine forms 5,7-dihydro-1-benzothiopyrano[4,3-*b*][1,5]benzodiazepine, with

⁷⁶ C. D. Hurd and R. I. Mori, *J. Amer. Chem. Soc.* **77**, 5359 (1955).

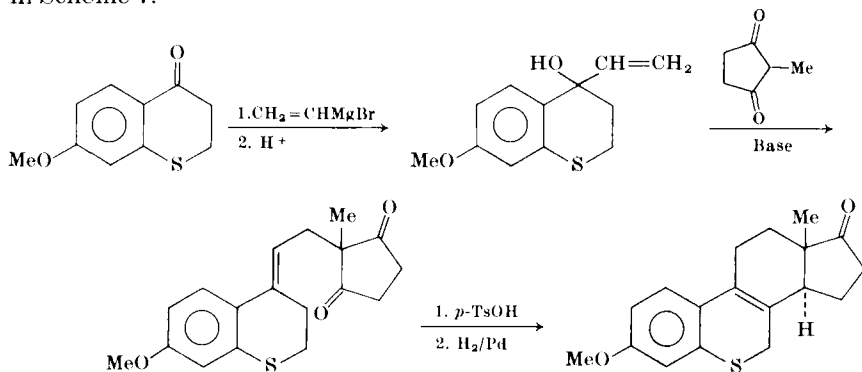
⁷⁷ A. Fravolini, A. Martani, and G. Grandolini, *Bol. Sci. Fac. Chim. Ind. Bologna* **26**, 269 (1968); *Chem. Abstr.* **70**, 106482 (1969).

hydroxylamine hydrochloride forms 4*H*-1-benzothiopyrano[3,4-*d*]isoxazole, with hydrazine hydrate forms 4*H*-1-benzothiopyrano[4,3-*c*]pyrazole, and with thiosemicarbazide forms 1-thiocarbamoyl-9*b*-hydroxy-3*a*,9*b*-dihydro-4*H*-1-benzothiopyrano[4,3-*c*]pyrazole.⁷⁷

Thiochroman-4-ones with malononitrile give the corresponding 4-ylidenemalononitriles,⁷⁸ which undergo disproportionation when cyclized by sulfuric acid [Eq. (13)], provided a 6-methyl substituent is present to prevent ring sulfonation in preference to annelation to the keto-amide.⁸⁰



Extensive synthetic work with 7-methoxythiochroman-4-one has led to a variety of 6-thio steroids, particularly thioestrogens,⁸¹⁻⁸⁵ as, e.g., in Scheme 7.⁸³



SCHEME 7

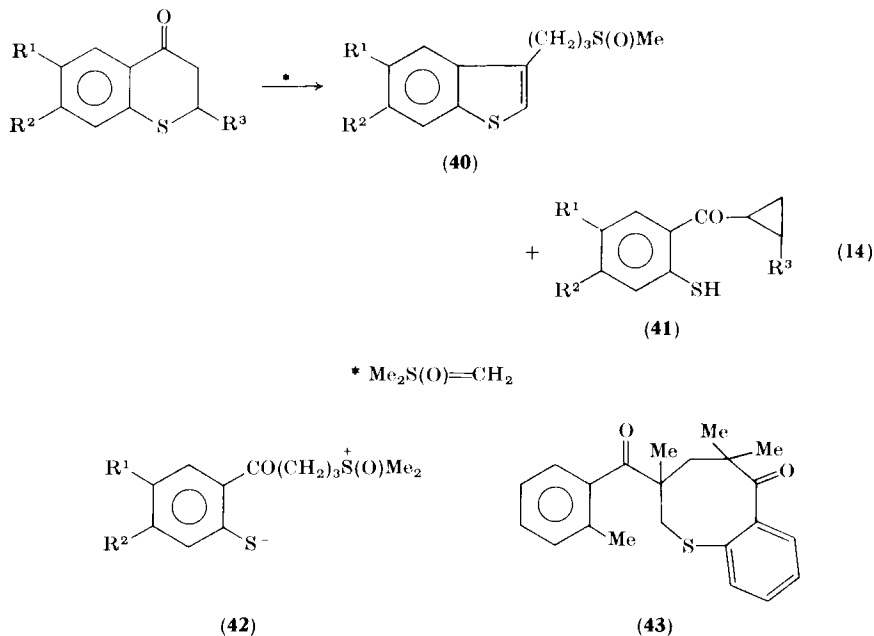
⁷⁸ E. Campaigne and C. D. Blanton, *Tetrahedron Lett.*, 2489 (1964).

⁷⁹ E. Campaigne, H. R. Burton, C. D. Blanton, and S. W. Schneller, *J. Heterocycl. Chem.*, **8**, 65 (1971).

⁸⁰ S. W. Schneller and F. W. Clough, *J. Heterocycl. Chem.*, **10**, 131 (1973).

⁸¹ J. G. Westra, W. N. Speekamp, U. K. Pandit, and H. O. Huisman, *Tetrahedron Lett.*, 2781 (1966).

Thiochroman-4-ones fragment on treatment with dimethylsulfoxonium methylide [Eq. (14)].⁸⁶ When $R^3 = H$, both **40** and **41** are produced at 50° whereas only **40** is obtained at room temperature; the process is believed to involve **42**. In a mechanistically similar reaction, 3-methylthiochroman-4-one yields 3,4,5,6-tetrahydro-3,5,5-trimethyl-3-[*o*-(methylthio)benzoyl]-2*H*-1-benzothiocrin-6-one (**43**).⁸⁷



Photochemical reactions of thiochroman-4-one give mainly polymeric products,⁸⁸ but irradiation of the corresponding sulfoxides⁸⁹ (**44**) and sulfones⁹⁰ (**45**) forms disulfides and pinacols [Eqs. (15) and (16)].

⁸² T. Moriwake, *J. Med. Chem.* **9**, 163 (1966).

⁸³ H. D. Huisman, J. G. Westra, W. N. Speckamp, and U. K. Pandit, U.S. Patent 3,417,100; *Chem. Abstr.* **70**, 47700 (1969).

⁸⁴ W. N. B. Koenst, J. L. Van-Bruynsvort, W. N. Speckamp, and H. O. Huisman, *Tetrahedron Lett.*, 2527 (1970).

⁸⁵ W. N. Speckamp, J. G. Westra, and H. O. Huisman, *Tetrahedron* **26**, 2353 (1970).

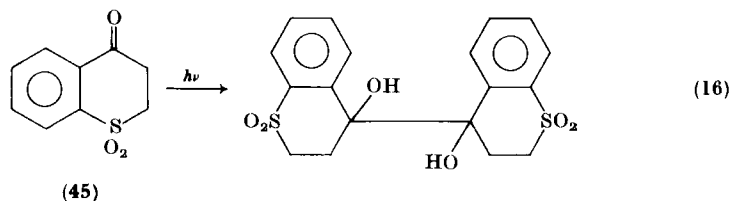
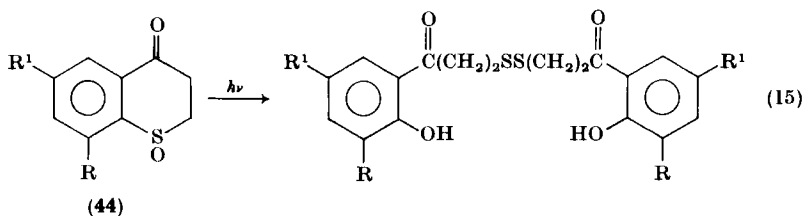
⁸⁶ W. N. Speckamp, J. Dijkink, J. A. Maassen, and H. O. Huisman, *Tetrahedron Lett.*, 2743 (1970).

⁸⁷ I. W. J. Still, M. S. Chauhan, and M. T. Thomas, *Can. J. Chem.* **51**, 839 (1973).

⁸⁸ P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.* **35**, 584 (1970).

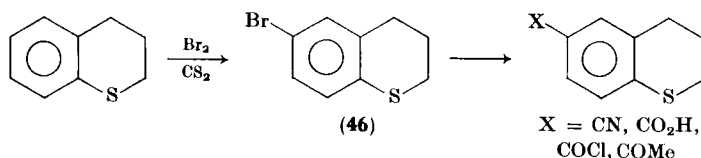
⁸⁹ I. W. J. Still, M. S. Chauhan, and M. T. Thomas, *Tetrahedron Lett.*, 1311 (1973).

⁹⁰ I. W. J. Still and M. T. Thomas, *J. Org. Chem.* **33**, 2730 (1968).



D. REACTIONS OF THIOCHROMANS

Bromination of thiochroman yields⁹¹ the 6-bromo compound (46) which has been converted into various 6-substituted derivatives (Scheme 8). Friedel-Crafts acylation also occurs at the 6-position.^{92,93} The *S,S*-dioxide with *N*-bromosuccinimide yields 4-bromothiochroman



SCHEME 8

1,1-dioxide.⁹⁴ The *S,S*-dioxides with zinc/hydrochloric acid/acetic acid reform the reduced thiochroman.⁹⁵ Treatment of the thiochromans with sulfur is a route to 1,4-dithiochromanones.^{96,97}

Morin, Spry, and Mueller⁹⁸ found that cyclic sulfoxides which do not possess an α -hydrogen undergo internal oxidation-reduction with oxidation of the carbon *beta* to the sulfur. Thus, 2,2-dimethylthio-

⁹¹ P. Cagniant and Mme. P. Cagniant, *C.R. Acad. Sci.* **231**, 1508 (1950).

⁹² P. Cagniant and Mme. P. Cagniant, *Bull. Soc. Chim. Fr.*, 1560 (1961).

⁹³ P. Cagniant and Mme. P. Cagniant, *C.R. Acad. Sci.* **253**, 1702 (1961).

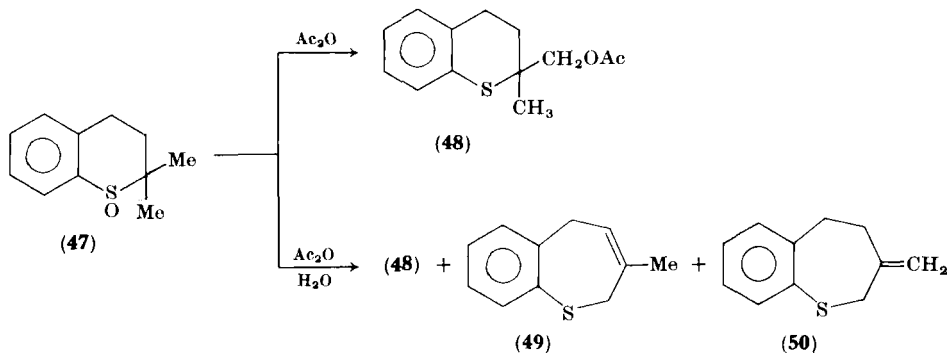
⁹⁴ F. J. Lotspeich, *J. Org. Chem.* **30**, 2068 (1965).

⁹⁵ F. G. Bordwell and W. H. McKellin, *J. Amer. Chem. Soc.* **73**, 2251 (1951).

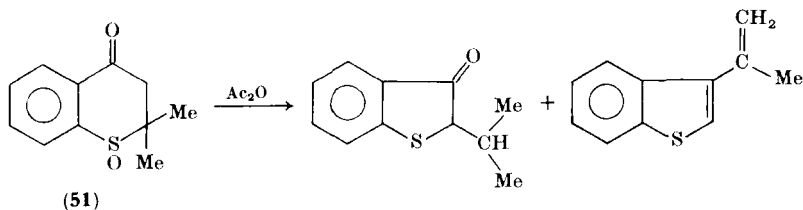
⁹⁶ R. Mayer, *Chem. Ber.* **90**, 2362 (1957).

⁹⁷ R. Mayer and H. Damme, *Z. Chem.* **5**, 150 (1965).

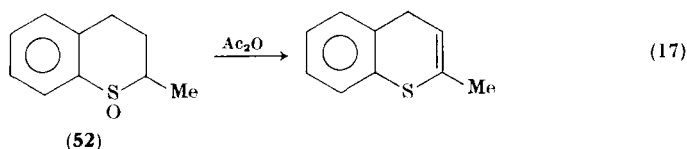
chroman 1-oxide (47) with acetic anhydride yields 48 whereas acetic anhydride/water gave 48 and the rearrangement products 49 and 50 (Scheme 9).⁹⁸ Scheme 10 shows the effect of a β -carbonyl group (51) on this rearrangement.⁹⁸ Cyclic sulfoxides with an α -hydrogen (e.g., 52) yield dehydration products via Pummerer rearrangement [Eq. (17)]. Photochemical rearrangement of 47 and 51 formed 2-isopropylbenzo[b]-



SCHEME 9



SCHEME 10



thiophene and 2-isopropylidenebenzo[b]thiophen-3-one, respectively.⁹⁹ Similar ring contraction of 3-bromothiochroman-4-ol to a benzo[b]-thiophene occurs¹⁰⁰ in aqueous dioxane.

⁹⁸ R. B. Morin, D. O. Spry, and R. A. Mueller, *Tetrahedron Lett.*, 849 (1969).

⁹⁹ R. A. Archer and B. S. Kitchell, *J. Amer. Chem. Soc.* **88**, 3462 (1966).

¹⁰⁰ H. Hofmann and G. Salbeck, *Angew. Chem., Int. Ed. Engl.* **8**, 456 (1969).

E. PHYSICOCHEMICAL PROPERTIES OF THIOCHROMAN-4-ONES AND THIOCHROMANS

The infrared spectra and dielectric constants,^{101,102} electronic,¹⁰³⁻¹¹¹ nuclear magnetic resonance (NMR),^{106,112-121} and mass¹²²⁻¹²⁶ spectral data for these compounds have been analyzed. There exist numerous quantum mechanical calculations of the electronic transitions and involvement of the sulfur electrons.^{107,111} Ultraviolet spectral determinations of the basicity of thiochroman-4-ones¹¹⁰ allowed correlations with the corresponding chroman-4-ones.

Nuclear magnetic resonance clarifies the conformation of the sulfur-containing ring. Thus 3-halogen substituents in thiochroman-4-ones are

- ¹⁰¹ G. F. Katekar and A. G. Moritz, *Aust. J. Chem.* **22**, 2337 (1969).
- ¹⁰² A. Lüttringhaus, R. Mecke, and J. Grohmann, *Elektronentheor. Homoeopolaren Bindung Hauptjahrestag. Chem. Ges. Deut. Demokrat. Repub.*, 152 (1955); *Chem. Abstr.* **53**, 3882 (1959).
- ¹⁰³ F. Krollpfeiffer, *Ber.* **58B**, 1677 (1925).
- ¹⁰⁴ M. J. Y. Foley and N. H. P. Smith, *J. Chem. Soc.*, 1899 (1963).
- ¹⁰⁵ E. Rakosi-David, R. Bognar, and M. Rakosi, *Acta Phys. Chim. Debrecina* **10**, 97 (1965); *Chem. Abstr.* **64**, 1494 (1966).
- ¹⁰⁶ D. Cagniant and P. Cagniant, *Bull. Soc. Chim. Fr.*, 228 (1966).
- ¹⁰⁷ J. Dehler, H. Giovanelli, W. Amann, and W. Schneider, *Ber. Bunsenges. Phys. Chem.* **71**, 655 (1967); *Chem. Abstr.* **68**, 25206 (1968).
- ¹⁰⁸ G. Kresze and W. Amann, *Spectrochim. Acta Part A* **25**, 393 (1969).
- ¹⁰⁹ G. Kresze and W. Amann, *Spectrochim. Acta Part A* **26**, 647 (1970).
- ¹¹⁰ D. E. Rakosi, M. Rakosi, J. Balint, and R. Bognar, *Acta Phys. Chim. Debrecina* **15/16**, 163 (1970); *Chem. Abstr.* **75**, 12884 (1971).
- ¹¹¹ K. H. Giovanelli, J. Dehler, and G. Hohlneicher, *Ber. Bunsenges. Phys. Chem.* **75**, 864 (1971); *Chem. Abstr.* **75**, 135180 (1971).
- ¹¹² M. M. Dhingra, G. Govil, C. L. Khetrpal, and V. M. Vaidya, *Tetrahedron Lett.*, 497 (1963).
- ¹¹³ G. F. Katekar and A. G. Moritz, *Aust. J. Chem.* **20**, 2235 (1967).
- ¹¹⁴ A. R. Katritzky and B. Ternai, *J. Heterocycl. Chem.* **5**, 745 (1968).
- ¹¹⁵ G. Grandolini, A. Ricci, N. P. Buu-Hoi, and F. Perin, *J. Heterocycl. Chem.* **5**, 133 (1968).
- ¹¹⁶ H. Hofmann and G. Salbeck, *Tetrahedron Lett.*, 2587 (1969).
- ¹¹⁷ G. Kresze and W. Amann, *Spectrochim. Acta Part A* **26**, 637 (1970).
- ¹¹⁸ M. Nishio, *Chem. Pharm. Bull.* **17**, 274 (1969).
- ¹¹⁹ G. F. Katekar, *J. Heterocycl. Chem.* **7**, 187 (1970).
- ¹²⁰ J. B. Lambert and F. R. Koeng, *Org. Magn. Reson.* **3**, 389 (1971).
- ¹²¹ A. Chatterjee and B. Bandyopadhyay, *Indian J. Chem.* **11**, 446 (1973).
- ¹²² B. D. Tilak, K. G. Das, and H. M. El-Namaky, *Experientia* **23**, 609 (1967).
- ¹²³ E. S. Brodskii, R. A. Khmel'nitskii, A. A. Polyakova, and G. D. Gel'pern, *Neftkhimiya* **9**, 146 (1969); *Chem. Abstr.* **71**, 2834 (1971).
- ¹²⁴ A. G. Harrison, M. T. Thomas, and I. W. J. Still, *Org. Mass. Spectrom.* **3**, 899 (1970).
- ¹²⁵ A. G. Loudon, A. Maccoll, and S. K. Wong, *J. Chem. Soc. B*, 1727 (1970).
- ¹²⁶ A. G. Loudon, A. Maccoll, and S. K. Wong, *J. Chem. Soc. B*, 1733 (1970).

pseudo axially oriented, but 3-methyl groups are pseudo equatorial.^{114,119,121} The vicinal coupling constants of the CH₂-CH₂ moiety indicate¹²⁰ the flattening of this ring. Finally, coupling between the H-3, H-4, and H-5 protons can be a valuable diagnostic indicator of the cis-trans orientation of substituents in the sulfur ring.¹¹⁶

Polarographic reduction¹²⁷ of thiochroman-4-one produces two waves, at 1.43 V and 1.31 V.

An X-ray analysis¹²⁸ of the clathrate¹²⁹ formed by 4-(*p*-hydroxyphenyl)-2,2,4-trimethylthiochroman has been reported.

F. USES OF THIOCHROMAN-4-ONES AND THIOCHROMANS

A variety of thiochromans possess biological activity. For example, 7-sulfamoylthiochroman 1,1-dioxides are effective diuretics;¹³⁰⁻¹³⁴ thiochroman-6-acetic acids possess antiinflammatory, antipyretic, and analgesic activity;^{135,136} phenethylamines from the Mannich reaction on thiochroman-4-ones are α -sympatholytic¹³⁷ and antidepressant;¹³⁸ 4-substituted aminothiochromans are active as antihypertensives, as antidepressants, and as agents against angina pains;¹³⁹⁻¹⁴² 3,3-dibromo-6-halothiochroman-4-one S-oxides exhibit antitumor characteristics;¹⁴³ substituted 4-phenylthiochroman-4-ols have been prepared

¹²⁷ C. Angelini and N. Fedi, *Boll. Chim. Farm.* **97**, 667 (1958); *Chem. Abstr.* **53**, 11061 (1959).

¹²⁸ D. D. MacNicol and F. B. Wilson, *J. Chem. Soc. D*, 786 (1971).

¹²⁹ D. D. MacNicol, *J. Chem. Soc. D*, 836 (1969).

¹³⁰ J. R. Boissier and C. Malen, French Patent 1,365,504; *Chem. Abstr.* **61**, 14642 (1964).

¹³¹ J. R. Boissier and C. Malen, French Patent M2790; *Chem. Abstr.* **62**, 9113 (1965).

¹³² J. R. Boissier, C. Dumont, J. Lesbros, and C. Malen, *Therapie* **20**, 1305 (1965).

¹³³ J. R. Boissier, C. Dumont, J. Lesbros, and D. Moisy, *Therapie* **22**, 137 (1967).

¹³⁴ J. R. Boissier, C. Dumont, and A. Geradin, *Ann. Pharm. Fr.* **28**, 497 (1970); *Chem. Abstr.* **74**, 86038 (1971).

¹³⁵ J. R. Boissier and R. Ratouis, French Patent 2,125,152; *Chem. Abstr.* **78**, 124449 (1973).

¹³⁶ J. R. Boissier and R. Ratouis, German Patent 2,106,045; *Chem. Abstr.* **75**, 151675 (1971).

¹³⁷ W. Hansen, German Patent 1,913,199; *Chem. Abstr.* **74**, 13005 (1971).

¹³⁸ M. Nakanishi, T. Munakata, and S. Setoguchi, German Patent 2,018,097; *Chem. Abstr.* **74**, 13006 (1971).

¹³⁹ G. deStevens, A. Halamandaris, P. Strachan, E. Donoghue, L. Dorfman, and C. F. Huebner, *J. Med. Chem.* **6**, 357 (1963).

¹⁴⁰ J. R. Boissier and R. Ratouis, French Patent M7499; *Chem. Abstr.* **75**, 35743 (1971).

¹⁴¹ J. R. Boissier and R. Ratouis, French Patent 1,584,755; *Chem. Abstr.* **74**, 111911 (1971).

as oral antifertility agents;¹⁴⁴ and a hydantoin possessing the thiochromanone nucleus appears to have anticonvulsant activity.¹⁴⁵

Many 3-dialkylaminomethyl- and 5-dialkylaminoalkylaminothiochroman-4-ones exhibit schistosomicidal activity,¹⁴⁶⁻¹⁴⁸ and a variety of other aminothiochromans are antiamebic.¹⁴⁹⁻¹⁵² The thiochroman ring is also found in antimicrobial agents,¹⁵³⁻¹⁵⁶ virucides,^{157,158} insecticides,¹⁵⁹ and acaricides,¹⁶⁰ and antiedemic¹⁶¹ and anti-inflammatory¹⁶² agents. Hexahydrothiochroman has been employed as a fuel additive,¹⁶³ and several *t*-butyl thiochroman-4-ones have been studied for their

¹⁴² C. Malen, B. Danree, and M. Laubie, German Patent 2,017,902; *Chem. Abstr.* **74**, 22698 (1971).

¹⁴³ M. Nishio, T. Ito, Y. Yamada, K. Nagaoka, and N. Kanagawa, German Patent 1,958,238; *Chem. Abstr.* **73**, 35224 (1970).

¹⁴⁴ R. R. Crenshaw, U.S. Patent 3,321,483; *Chem. Abstr.* **68**, 29601 (1968).

¹⁴⁵ H. Arnold, E. Kuehas, and N. Brock, German Patent 1,135,915; *Chem. Abstr.* **58**, 3439 (1963).

¹⁴⁶ S.-L. Chu and C.-C. Chang, *Hua Hsueh Hsueh Pao*, **24**, 87 (1958); *Chem. Abstr.* **53**, 7160 (1959).

¹⁴⁷ S.-L. Chu, W.-H. Chyan, and C.-C. Chang, *Hua Hsueh Hsueh Pao* **22**, 371 (1956); *Chem. Abstr.* **52**, 11044 (1958).

¹⁴⁸ F. Bossert and R. Goennert, *Med. Chem., Abbandl. Med.-Chem. Forschungsstaetten Hoechst. A.G.* **1**, 367 (1963); *Chem. Abstr.* **60**, 9236 (1964).

¹⁴⁹ A. B. Sen and Y. D. Kulkarni, *J. Indian Chem. Soc.* **34**, 687 (1957).

¹⁵⁰ B. S. Kaushiva, *Ann. Biochem. Exp. Med.* **20**, 493 (1960); *Chem. Abstr.* **58**, 8254 (1963).

¹⁵¹ A. B. Sen and S. B. Singh, *J. Indian Chem. Soc.* **43**, 521 (1966).

¹⁵² A. Mishra, A. Nayak, and M. K. Rout, *J. Inst. Chem., Calcutta* **42**, 223 (1970); *Chem. Abstr.* **74**, 108592 (1971).

¹⁵³ H. A. Wagner, U.S. Patent 3,158,619; *Chem. Abstr.* **62**, 7748 (1965).

¹⁵⁴ J. Crutze, K. Thomas, and D. Jerchel, South African Patent 6,808,173; *Chem. Abstr.* **72**, 90290 (1970).

¹⁵⁵ T. Ishii, and S. Ito, Japan Patent 7,019,299; *Chem. Abstr.* **73**, 66426 (1970).

¹⁵⁶ C. Rufer, R. Albrecht, H. J. Kessler, and E. Schroeder, German Patent 1,935,685; *Chem. Abstr.* **74**, 100049 (1971).

¹⁵⁷ R. Albrecht, M. Muftir, and E. Schroeder, South African Patent 6,805,902; *Chem. Abstr.* **72**, 12551 (1970).

¹⁵⁸ M. Nishio, S. Ito, and N. Ishida, Japan Patent 7,013,816; *Chem. Abstr.* **73**, 45350 (1970).

¹⁵⁹ G. Hoerlein, G. Salbeck, K. D. Bock, and L. Emmel, German Patent 2,148,879; *Chem. Abstr.* **78**, 159431 (1973).

¹⁶⁰ M. D. Barker, German Patent 1,915,496; *Chem. Abstr.* **72**, 66799 (1970).

¹⁶¹ M. Nishio, T. Koeda, T. Ito, and U. Shibata, German Patent 1,933,523; *Chem. Abstr.* **75**, 5709 (1971).

¹⁶² M. Nishio, K. Ichuime, T. Ito, T. Koeda and U. Shibata, Japan Patent 7,026,099; *Chem. Abstr.* **73**, 130890 (1970).

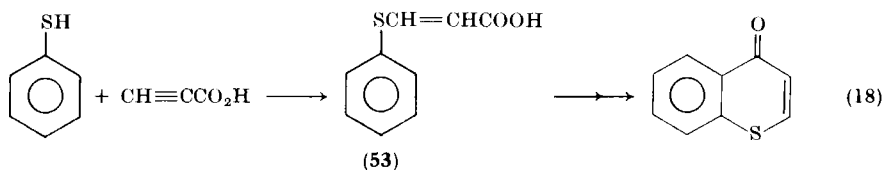
¹⁶³ R. A. Vere, *AGARD Conf. Proc. 1971, AGARD -CP-84-71, 11-1-1-13*; *Chem. Abstr.* **75**, 142483 (1971).

odoriferous^{164,165} characteristics (the vapors of 6-*t*-butyl- and 6-*t*-butyl-8-methylthiochroman-4-ones resemble burning sandalwood¹⁶⁴). Thiochromans are found in some resins¹⁶⁶ and dyes,¹⁶⁷ thiochroman S-oxide has been used in uranium extractions,¹⁶⁸ and 4-(*p*-hydroxyphenyl)-2,2,4-trimethylthiochroman forms a clathrate¹²⁹ with many solvents, usually in a 3:1 host to guest ratio for small molecules (ethanol or acetone) and 6:1 for larger molecules (e.g., toluene).

III. Thiochromones

A. PREPARATION OF THIOCHROMONES

Two principal routes yield thiochromones. The first involves Michael addition of a thiophenol to a propiolic acid, followed by Friedel-Crafts cyclization of the chloride of the resultant β -phenylmercaptoacrylic acid¹⁶⁹⁻¹⁷⁴ [Eq. (18)]. The preferred cyclization catalyst is stannic



chloride (aluminum chloride can yield thiocoumarins¹⁷⁴) or a mixture of phosphorus pentoxide and phosphoric acid. The acrylic acid (53) has also been prepared by direct nucleophilic displacement of a chloride ion by thiophenol on β -chloroacrylic acid¹⁷¹ or of an ethoxide ion by

¹⁶⁴ N. P. Buu-Hoi, V. Bellavita, A. Ricci, and D. Balucani, *Bull. Soc. Chim. Fr.*, 1210 (1966).

¹⁶⁵ A. Ricci and N. P. Buu-Hoi, *Bull. Soc. Chim. Fr.*, 3634 (1967).

¹⁶⁶ H. S. Bloch and H. E. Mammen, U.S. Patent 2,657,193; *Chem. Abstr.* **48**, 3724 (1958).

¹⁶⁷ F. Arndt, W. Flemming, E. Scholz, and V. Lowensohn, *Ber.* **56B**, 1269 (1923).

¹⁶⁸ A. M. Rozen, Yu. I. Murinov, and Yu. E. Nikitin, *Radiokhimiya* **12**, 355 (1970); *Chem. Abstr.* **73**, 49060 (1970).

¹⁶⁹ S. Ruhemann, *Ber.* **46**, 2188 (1913).

¹⁷⁰ S. Ruhemann, *Ber.* **46**, 3384 (1913).

¹⁷¹ S. Ruhemann, *Ber.* **47**, 119 (1914).

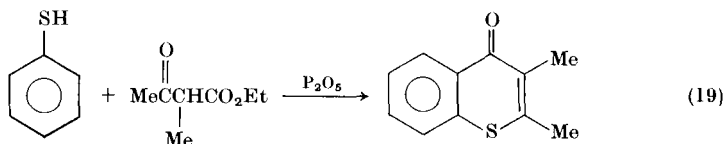
¹⁷² F. Montanari and A. Negrini, *Boll. Sci. Fac. Chim. Ind. Bologna* **15**, 50 (1957); *Chem. Abstr.* **51**, 16451 (1957).

¹⁷³ W. E. Truce and D. L. Goldhamer, *J. Amer. Chem. Soc.* **81**, 5795 (1959).

¹⁷⁴ N. Lozac'h, L. Legrand, and N. Bigneat, *Bull. Soc. Chim. Fr.* **12**, 3247 (1964).

thiophenol on ethyl β -ethoxyacrylate^{175,176} (to yield the corresponding β -arylthioacrylate).

The second general method into the thiochrom-4-one ring involves the interaction of a thiophenol with compounds possessing a carbon atom bonded by at least two electron withdrawing groups, usually in the presence of a dehydrating agent (phosphorus pentoxide or polyphosphoric acid). The first application of this was by Simonis and Elias¹⁷⁷ and is illustrated in Eq. (19). The most successful active methylene substrates have been β -ketoesters,¹⁷⁷⁻¹⁸² β -cyanoketones,¹⁸³



diacylacetic acids,¹⁸⁴ acylmalonic acid esters,¹⁸⁵ half-esters of malonic acid,¹⁸⁶ and α -acetamido- β -ketoesters.¹⁸⁷ With this array of possibilities a variety of thiochromones substituted in the sulfur ring is possible. Additionally, by changing the thiophenolic portion various benzo substituents can be realized.

Thiochrom-4-ones have also been prepared by the amine-promoted elimination of hydrogen halide from 3-halothiochroman-4-ones,¹⁸⁸ by the Pummerer reaction on thiochroman-4-one S-oxides [Eq. (20)],⁹⁸ from a ring expansion of activated benz[*b*]thiophenes [Eq. (21)],¹⁸⁹ by the reaction of *o*-mercaptoaryl alkyl ketones with ethyl esters of

¹⁷⁵ W. J. Croxall and L. R. Freimiller, U.S. Patent 2,532,291; *Chem. Abstr.* **45**, 3421 (1951).

¹⁷⁶ L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 953 (1958).

¹⁷⁷ H. Simonis and A. Elias, *Ber.* **49**, 768 (1916).

¹⁷⁸ Farbenfabriken Bayer Akt.-Ges., British Patent 803,803; *Chem. Abstr.* **53**, 11412 (1959).

¹⁷⁹ F. Bossert and H. Hanecka, German Patent 1,089,773; *Chem. Abstr.* **55**, 27379 (1961).

¹⁸⁰ F. Bossert, *Justus Liebigs Ann. Chem.* **680**, 40 (1964).

¹⁸¹ H. Simonis and A. Elias, *J. Chem. Soc.* **110**, 499 (1916).

¹⁸² F. Sauter and P. Stuetz, *Monatsh. Chem.* **98**, 1962 (1967).

¹⁸³ F. Bossert, *Tetrahedron Lett.*, 4377 (1968).

¹⁸⁴ Farbenfabriken Bayer Akt.-Ges., British Patent 804,689; *Chem. Abstr.* **53**, 11413 (1959).

¹⁸⁵ F. Bossert, German Patent 1,095,842; *Chem. Abstr.* **57**, 11170 (1962).

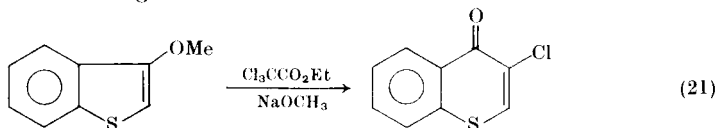
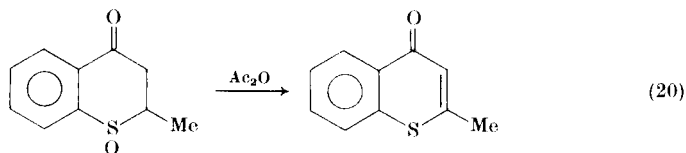
¹⁸⁶ A. Ruwet, A. Pourveur, and M. Renson, *Bull. Soc. Chim. Belge* **79**, 631 (1970).

¹⁸⁷ F. Bossert, *Tetrahedron Lett.*, 555 (1971).

¹⁸⁸ F. Arndt, *Ber.* **58B**, 2702 (1925).

¹⁸⁹ D. G. Hawthorne and Q. N. Porter, *Aust. J. Chem.* **19**, 1751 (1966).

aliphatic or aromatic acids in the presence of sodium hydride,¹⁹⁰ from the rearrangements of dihydrothiocoumarins,¹⁹¹ and by the condensation of thiophenolic ethers with benzaldehyde.¹⁹²



B. REACTIONS OF THIOCHROMONES

Thiochromones are readily brominated to the corresponding 2,3-dibromothiochroman-4-ones,^{177,193} which are transformed back to thiochromones in water.¹⁷⁷ Boiling alkalis rupture the sulfur ring of thiochromones to form *o*-mercaptobenzoic acids;¹⁷⁷ phosphorus pentasulfide forms the thioketone analog [Eq. (22)]. Furthermore, thiochromones undergo typical condensation reactions^{194,195} at the carbonyl center (usually after conversion into the thioketone) as in the preparation of the esters (54); they form the 4,4-dichloro-4*H*-1-benzothiopyran (55) in the presence of dichloromethyl methyl ether,¹⁹⁶ thionyl chloride,^{197,198} and oxalyl chloride.¹⁹⁹ The chlorine atoms 55 are easily displaced by nucleophiles^{196,198} or removed by copper bronze to yield^{197,199} di(thioflavylenes). Lewis acids convert thiochromones into thiocoumarins²⁰⁰ while alkylation affords 4-alkoxy-1-benzothiopyrylium salts [Eq. (23)].²⁰¹

¹⁹⁰ G. Jongebreur, *Pharm. Weekbl.* **86**, 661 (1951); *Chem. Abstr.* **47**, 2172 (1953).

¹⁹¹ G. Herbertz, H. Wamhoff, and F. Korte, *Z. Naturforsch. B* **23**, 312 (1968).

¹⁹² K. Auwers and F. Arndt, *Ber.* **42**, 2706 (1909).

¹⁹³ T. J. Speaker and P. J. Jannke, *J. Pharm. Sci.* **54**, 1073 (1965).

¹⁹⁴ A. Schoenberg and E. Frese, *Ber.* **96**, 2420 (1963).

¹⁹⁵ E. Frese, German Patent 1,241,438; *Chem. Abstr.* **68**, 68887 (1968).

¹⁹⁶ I. Farkas, B. Costisella, M. Rakosi, H. Gross, and R. Bognar, *Chem. Ber.* **102**, 1333 (1969).

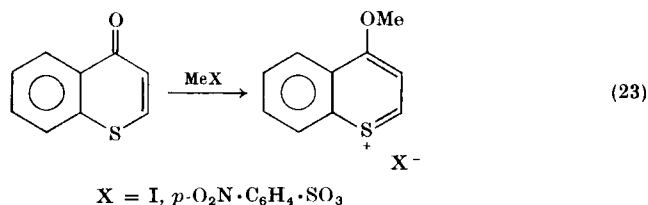
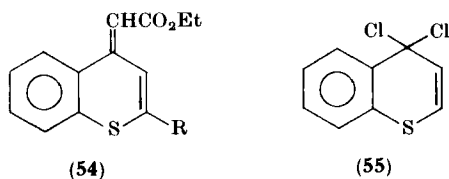
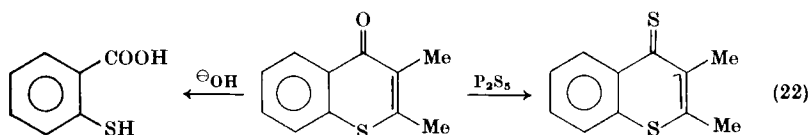
¹⁹⁷ A. Schönberg and W. Asker, *J. Chem. Soc.*, 272 (1942).

¹⁹⁸ K. Junghans and A. Schoenberg, German Patent 1,295,548; *Chem. Abstr.* **71**, 38826 (1969).

¹⁹⁹ A. Schönberg and S. Nickel, *Ber.* **67B**, 1795 (1934).

²⁰⁰ G. P. Guillouzo and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1624 (1962).

²⁰¹ A. I. Kiprianov and A. I. Tolmachev, *Zh. Obshch. Khim.* **29**, 2868 (1959); *Chem. Abstr.* **54**, 12126 (1960).



C. PHYSICOCHEMICAL PROPERTIES OF THIOCHROMONES

Infrared evidence of bond strengths and charge distributions²⁰² have been compared with similar data for 1-thiocoumarin, 1-selenocoumarin, 2-thiocoumarin, and 2-selenocoumarin.²⁰³ Ultraviolet data²⁰⁴ have been correlated with extensive molecular orbital calculations.²⁰⁵⁻²⁰⁹ Such calculations²⁰⁹ indicate that electrophilic substitution should occur at C-3 and nucleophilic or radical substitution at C-2. Nuclear magnetic resonance^{210,211} and mass spectral²¹² data are available. As

²⁰² R. Mecke, R. Mecke, and A. Lüttringhaus, *Z. Naturforsch. B* **10**, 367 (1955).

²⁰³ A. Ruwet and M. Renson, *Bull. Soc. Chim. Belge* **79**, 89 (1970).

²⁰⁴ J. Schmutz, H. Lauener, R. Hirt, and M. Sanz, *Helv. Chim. Acta* **34**, 767 (1951).

²⁰⁵ J. Fabian, A. Mehlhorn, and R. Mayer, *Z. Chem.* **5**, 22 (1965).

²⁰⁶ P. H. Given, S. Guha, J. R. Jones, and R. Wedel, *Nature (London)* **206**, 184 (1965).

²⁰⁷ J. Fabian, A. Mehlhorn, J. Bormann, and R. Mayer, *Wiss. Z. Tech. Univ. Dresden* **14**, 285 (1965); *Chem. Abstr.* **64**, 9072 (1966).

²⁰⁸ G. Kresze and W. Amann, *Spectrochim. Acta Part A* **24**, 1283 (1968); *Chem. Abstr.* **69**, 72434 (1968).

²⁰⁹ A. I. Tolmachev, G. G. Dyadyusha, and L. M. Shulezhko, *Teor. Eksp. Khim.* **6**, 185 (1970); *Chem. Abstr.* **73**, 55511 (1970).

²¹⁰ R. H. Martin, N. Defay, F. Geerts-Evard, P. H. Given, J. R. Jones, and R. W. Wedel, *Tetrahedron* **21**, 1833 (1965).

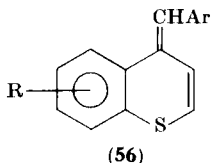
²¹¹ G. Kresze and W. Amann, *Spectrochim. Acta Part A* **26**, 637 (1970); *Chem. Abstr.* **72**, 131894 (1970).

²¹² D. Schumann, E. Frese, and A. Schoenberg, *Chem. Ber.* **102**, 3192 (1969).

in the thiochroman-4-one case (Section II,E), thiochrom-4-one *S,S*-dioxide exhibits two polarographic waves (-0.431 V and -1.096 V) assigned to reduction of the 2,3-double bond (first wave) and reduction of the carbonyl (second wave).²¹³ Spectrophotometric values have been determined for many thiochromones.^{214,215} The variation in the rates of hydrogen exchange at the 3-, 6-, and 8-positions of thiochromone has been evaluated as a function of the acidity of the medium.²¹⁶

D. USES OF THIOCHROMONES

A very significant application of thiochromones is the preparation of materials related to cyanine dyes^{217,218} and pigments.²¹⁹ The thiochromone ring system has been incorporated into schistosomicidal²²⁰⁻²²⁵ and bacteriostatic agents²²⁶ and into materials potentially useful in the treatment of arterial pressure and systolic discharge,²²⁷ capillary brittleness,²²⁸ allergic asthma and anaphylaxis,^{229,230} and hypotension.²³¹ Structures of the type **56** have been prepared from thiochromones for their potential estrogenic and antiestrogenic activity.²³²

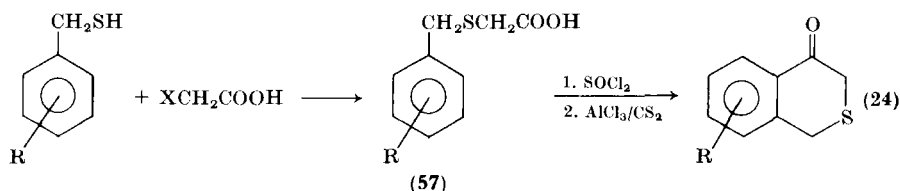


- ²¹³ N. Shinriki, *Yakugaku Zasshi* **88**, 1529 (1968); *Chem. Abstr.* **70**, 73558 (1969).
²¹⁴ A. I. Tolmachev, L. M. Sulezhko, and A. A. Kisilenko, *Zh. Obshch. Khim.* **37**, 367 (1967); *Chem. Abstr.* **67**, 53984 (1967).
²¹⁵ I. Degani, R. Fochi, and G. Sputa, *Boll. Sci. Fac. Chim. Ind. Bologna* **26**, 3 (1968); *Chem. Abstr.* **70**, 3131 (1969).
²¹⁶ A. R. Katritzky, U. Bressel, and J. R. Lea, *J. Chem. Soc. B.*, 11 (1971).
²¹⁷ A. I. Tolmachev and V. P. Stribnaya, *Zh. Obshch. Khim.* **32**, 383 (1962); *Chem. Abstr.* **58**, 1446 (1963).
²¹⁸ A. I. Tolmachev, *Zh. Obshch. Khim.* **30**, 2884 (1960); *Chem. Abstr.* **55**, 16538 (1961).
²¹⁹ D. G. Wilkinson, British Patent 851,571; *Chem. Abstr.* **55**, 10917 (1961).
²²⁰ F. Bossert and R. Gonnert, German Patent 954,599; *Chem. Abstr.* **53**, 6257 (1959).
²²¹ Farbenfabriken Bayer A.-G., British Patent 805,870; *Chem. Abstr.* **53**, 12306 (1959).
²²² F. Bossert, H. Henecka, and R. Gonnert, German Patent 1,024,981; *Chem. Abstr.* **54**, 7740 (1960).
²²³ R. Gonnert, *Bull. WHO* **25**, 702 (1961).
²²⁴ R. Gonnert and H. Koelling, *Drugs, Parasites, Hosts, Symp., Middlesex Hosp. Med. School*, **29** (1962); *Chem. Abstr.* **60**, 7349 (1964).
²²⁵ J. Pellegrino and J. Faria, *Amer. J. Trop. Med. Hyg.* **14**, 363 (1965); *Chem. Abstr.* **63**, 1084 (1965).

IV. Isothiochromans and Isothiochromanones

A. PREPARATION OF ISOTHIUCHROMANONES AND ISOTHIUCHROMANS

Reaction between benzylmercaptans and haloacetic acids yield benzylmercaptoacetic acids (**57**) which, via their acid chlorides, undergo an intramolecular Friedel-Crafts cyclization to produce isothiochromanones as in Eq. (24).²³³⁻²³⁵ Attempts to cyclize **57** with sulfuric acid,



as in the conversion of β -arylmercaptopropionic acids into thiochroman-4-ones, produced resinous materials,²³³ a characteristic of isothiochromanones in strong acid. Homoxilylene dibromide²³⁶ (**58**) with potassium sulfide conveniently yields isothiochroman.²³⁶⁻²⁴⁰ Two further preparative routes to isothiochromans involve a Friedel-Crafts procedure

²²⁶ T. Nambara, Y. Takemori, and S. Okamoto, *Yakugaku Zasshi* **81**, 1 (1961); *Chem. Abstr.* **55**, 12392 (1961).

²²⁷ C. Malen, B. Danree, and M. Laubrie, German Patent 2,017,902; *Chem. Abstr.* **74**, 22698 (1971).

²²⁸ C. Malen and P. Sesnoyers, British Patent 1,158,473; *Chem. Abstr.* **72**, 43450 (1970).

²²⁹ R. Hazard and J. King, German Patent 2,004,125; *Chem. Abstr.* **73**, 77057 (1970).

²³⁰ R. Hazard and J. King, German Patent 2,006,196; *Chem. Abstr.* **74**, 42279 (1971).

²³¹ G. Jongebreuer, *Arch. Int. Pharmacodyn.* **90**, 384 (1952); *Chem. Abstr.* **47**, 760 (1953).

²³² J. H. Fried, U.S. Patent 3,506,654; *Chem. Abstr.* **73**, 3812 (1970).

²³³ P. Cagniant and P. Cagniant, *Bull. Soc. Chim. Fr.*, 1998 (1959).

²³⁴ R. Lesser and A. Mehrlander, *Ber.* **56B**, 1642 (1923).

²³⁵ Bristol-Meyers Co., Netherlands Patent 6,510,990; *Chem. Abstr.* **65**, 8881 (1966).

²³⁶ J. V. Braun and F. Zobel, *Ber.* **56B**, 2142 (1923).

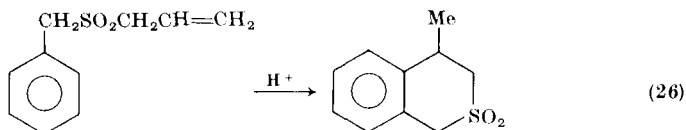
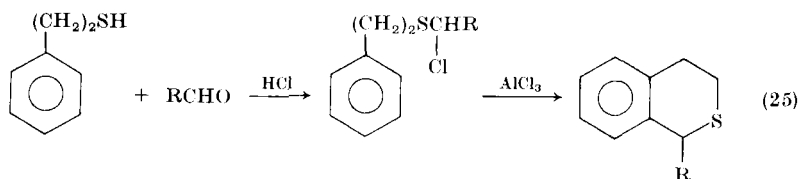
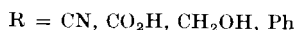
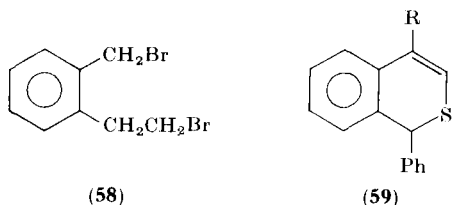
²³⁷ F. G. Holliman and F. G. Mann, *J. Chem. Soc.*, **34** (1945).

²³⁸ S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Inst. Petrol.* **40**, 76 (1954).

²³⁹ J. A. Faust and M. Sahyun, U.S. Patent 3,438,995; *Chem. Abstr.* **71**, 13126 (1969).

²⁴⁰ S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.* **19**, 1449 (1954).

[Eq. (25)],²⁴¹ and an acid-promoted olefin cyclization [Eq. (26)].²⁴²⁻²⁴⁴ Finally, the photocycloaddition of thiobenzophenone with propiolic acids produced the 1-phenyl compounds **59**.²⁴⁵



B. REACTIONS OF ISOTHIOCHROMANONES AND ISOTHIOCHROMANS

1. Isothiochromanones

Wolff-Kishner reduction of isothiochromanone²³³ gives the expected isothiochroman; for Clemmensen conditions, conflicting reports indicate isothiochroman²³⁸ or 1,3-dihydro-1-methylbenzo[c]thiophene²⁴⁶ as the products. Bromination may produce 3-bromoisothiochromanone, although this is not certain,²³⁴ while Grignard reagents²³⁵ yield 4-substituted isothiochroman-4-ol. Scheme 11 summarizes other reactions of this ketone and indicates its versatility as a starting material.²⁴⁶

²⁴¹ H. Boehme, L. Tils, and B. Unterhalt, *Ber.* **97**, 179 (1964).

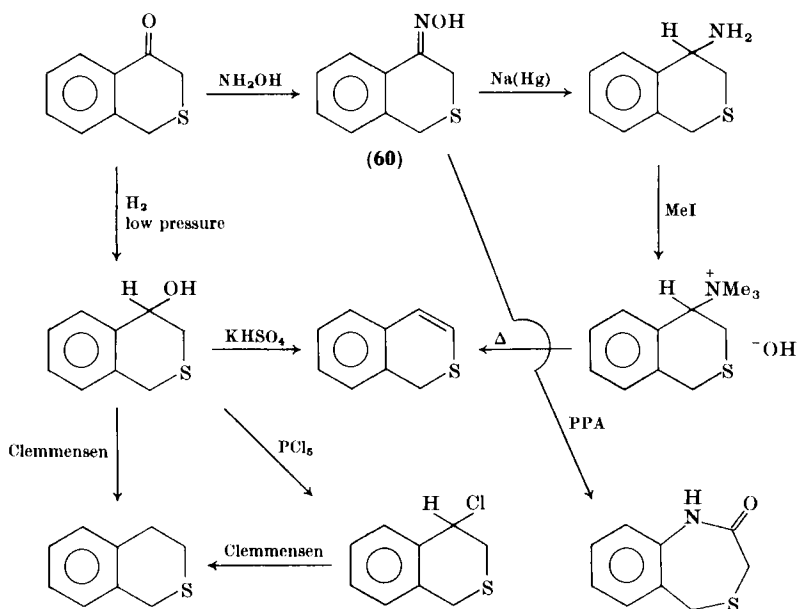
²⁴² H. J. Baker and N. Dost, *Rec. Trav. Chim.* **68**, 1143 (1949).

²⁴³ H. J. Baker and G. J. deJong, *Rec. Trav. Chim.* **70**, 377 (1951).

²⁴⁴ E. N. Karaulova, D. Sh. Meilanova, and G. D. Gal'pern, *Khim. Seraorg. Soedin.*, *Soderzh. Neft'yakh Nefteprod.*, *Akad. Nauk SSSR., Bashkir. Filial., Dokl. 3-ei (Tret'ei) Nauch. Sessii, Ufa*, 164 (1957); *Chem. Abstr.* **55**, 1497 (1961).

²⁴⁵ A. Ohno, T. Koizumi, Y. Ohnishi, and G. Tsuchihashi, Japan Patent 7,301,077; *Chem. Abstr.* **78**, 147802 (1973).

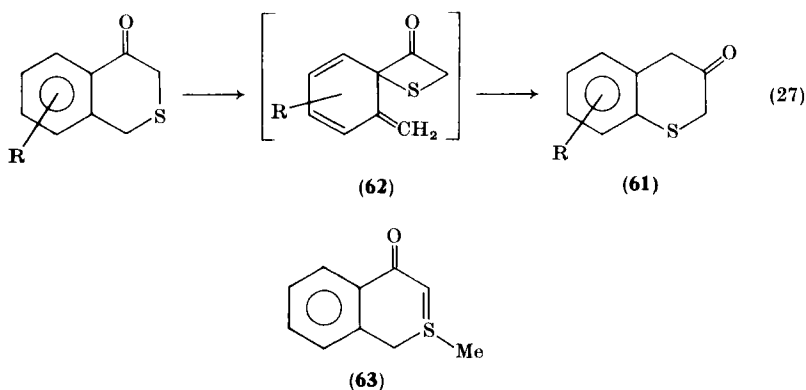
²⁴⁶ J. V. Braun and K. Weissbach, *Ber.* **62B**, 2416 (1929).



SCHEME 11

The oxime (60) (Scheme 11) undergoes the Beckmann rearrangement to 3,5-dihydro-4,1-benzothiazepin-2(1*H*)-one.²⁴⁷

Several isothiochroman-4-ones rearrange photochemically to thiochroman-3-ones (61) via the intermediate spiro-thietan-3-one (62) [Eq. (27)].^{248,249} The ylid (63) is transformed into 1-indanone²⁵⁰ photochemically.



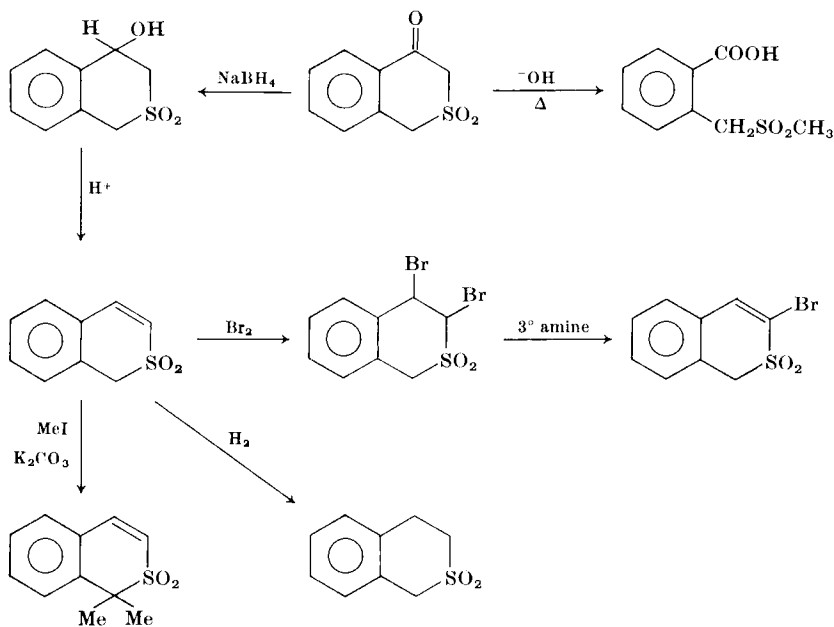
²⁴⁷ R. K. Hill and D. A. Cullisen, *J. Amer. Chem. Soc.* **95**, 2923 (1973).

²⁴⁸ W. C. Lumma and G. A. Berchtold, *J. Amer. Chem. Soc.* **89**, 2761 (1967).

²⁴⁹ W. C. Lumma and G. A. Berchtold, *J. Org. Chem.* **34**, 34 (1969).

²⁵⁰ R. H. Fish, L. C. Chow, and M. C. Caserio, *Tetrahedron Lett.*, 1259 (1969).

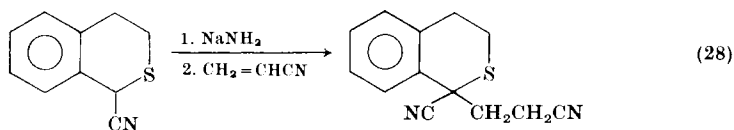
Isothiochromanone is easily oxidized to its *S,S*-dioxide using potassium permanganate.²⁵⁷ Reactions of this sulfone are shown in Scheme 12.²⁵¹



SCHEME 12

2. Isothiochromans

Chlorination or bromination of isothiochroman yields the corresponding 1-halo derivatives,^{241,252,253} which are intermediates for numerous isothiochromans since the halogen atoms are benzylic and, therefore, very susceptible to nucleophilic substitution. Thus, 1-chloroisothiochroman with mercuric cyanide gives the 1-cyano derivative, which provides the 1-carboxylic acid, 1-ester, and the 1-amide.^{239,252} The remaining 1-H of the 1-cyano derivative is acidic and, with base,



²⁵¹ G. Pagani and S. Maiorana, *Chim. Ind. (Milan)* **49**, 1347 (1967); *Chem. Abstr.* **69**, 2814 (1968).

²⁵² H. Boehme, L. Tils, and B. Unterhalt, *Arch. Pharm. (Weinheim)* **297**, 325 (1964); *Chem. Abstr.* **61**, 8265 (1964).

²⁵³ H. Boehme, R. Priesner, and B. Unterhalt, *Arch. Pharm. (Weinheim)* **299**, 931 (1966); *Chem. Abstr.* **66**, 37728 (1967).

forms a potent nucleophile susceptible to the usual reactions, e. g., as in Eq. (28), to produce materials useful in further synthesis.²⁵³⁻²⁵⁷

Isothiochroman undergoes simple alkylation at the sulfur to form sulfonium salts,²³⁷ is ring-opened and desulfurized with Raney nickel,²⁴⁴ and is ring-opened to 2-(*o*-tolyl)ethyl mercaptan with $\text{Ca}(\text{NH}_3)_6$.²⁵⁸

C. PHYSICOCHEMICAL PROPERTIES OF ISOTHIUCHROMANS

X-ray analysis demonstrates the boat conformation is preferred for isothiochroman *S,S*-dioxides.^{259,260} Ultraviolet,²⁶¹ NMR,²⁶² and mass spectral²⁶³ data have also been reported.

D. USES OF ISOTHIUCHROMANS

1-Substituted and 1,1-disubstituted derivatives synthesized as discussed in Section IV,B,2 possess potential biological (antitussive,^{256,264} sedative,²⁶⁵ muscle relaxant²⁶⁵) activity.^{239,255,257}

V. Benzothiopyrans

A. PREPARATION OF 2*H*-1-BENZOTHIOPYRANS

Dehydration of thiochroman-4-ols, generally with potassium hydrogen sulfate, is the most convenient preparation of 2*H*-1-benzothiopyrans,^{266,267} [Eq. (29)]. Further methods to derivatives of **4** involve the Vilsmeier formylation of thiochroman-4-one to β -chlorovinyl aldehydes

²⁵⁴ H. Boehme and K. Lindenberg, *Arch. Pharm. (Weinheim)* **301**, 544 (1968); *Chem. Abstr.* **69**, 106524 (1968).

²⁵⁵ H. Boehme, K. Lindenberg, and B. Unterhalt, *Arch. Pharm. (Weinheim)* **301**, 580 (1968); *Chem. Abstr.* **69**, 106452 (1968).

²⁵⁶ H. Boehme, K. Lindenberg, R. Priesner, and B. Unterhalt, *Arch. Pharm. (Weinheim)* **301**, 326 (1968); *Chem. Abstr.* **69**, 51937 (1968).

²⁵⁷ H. Boehme and K. Lindenberg, *Arch. Pharm. (Weinheim)* **303**, 229 (1970); *Chem. Abstr.* **73**, 14621 (1970).

²⁵⁸ J. van Schooten, J. Knotnerus, H. Boer, and P. M. Duinker, *Rec. Trav. Chim.* **77**, 935 (1958).

²⁵⁹ D. A. Whiting and D. A. Pulman, *J. Chem. Soc. D.*, 831 (1971).

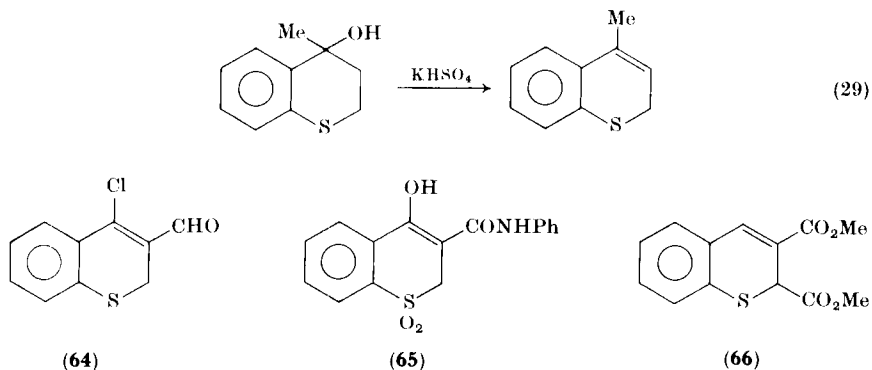
²⁶⁰ D. A. Pulman and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 410 (1973).

²⁶¹ V. Georgian, *Chem. Ind. (London)*, 1480 (1957).

²⁶² S. H. Smallcombe, R. J. Holland, R. H. Fish, and M. C. Caserio, *Tetrahedron Lett.*, 5987 (1968).

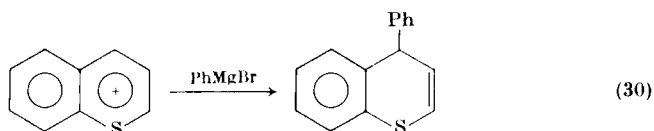
²⁶³ P. Natalis, *Bull. Cl. Sci., Acad. Roy. Belg.* **48**, 554 (1962); *Chem. Abstr.* **58**, 405 (1963).

of the type **64**,²⁶⁸ treatment of thiochroman-4-one *S,S*-dioxide with sodium hydride followed by phenyl isocyanate resulting in **65**,²⁶⁹ the cycloaddition of dimethyl acetylenedicarboxylate with cycloheptatriene-thione forming the diester **66**,²⁷⁰ and the reaction of aromatic amines²⁷¹ and thiols²⁷² with 1-benzothiopyrylium salts.



B. PREPARATION OF 4*H*-1-BENZOTHIOPYRANS

Aryl Grignard reagents with 1-benzothiopyrylium salts yield 4*H*-1-benzothiopyrans [Eq. (30)].²⁷¹ As mentioned in Section II,D, Pummerer



reaction conditions convert 2-methylthiochroman *S*-oxide into 2-methyl-4*H*-1-benzothiopyran⁹⁸ while 4*H*-1-benzothiopyrans have been

²⁶⁴ H. Boehme, German Patent 1,215,727; *Chem. Abstr.* **65**, 15337 (1966).

²⁶⁵ H. Boehme and K. Lindenberg, *Arch. Pharm. (Weinheim)* **301**, 584 (1968); *Chem. Abstr.* **70**, 3764 (1969).

²⁶⁶ M. M. Dhingra, G. Govil, C. L. Khatri, and V. M. Vaidya, *Tetrahedron Lett.*, 497 (1963).

²⁶⁷ S. Rossi and G. Pagani, *Tetrahedron Lett.*, 2129 (1966).

²⁶⁸ M. Weissenfels, H. Schurig, and G. Huehsam, *Z. Chem.* **6**, 471 (1966).

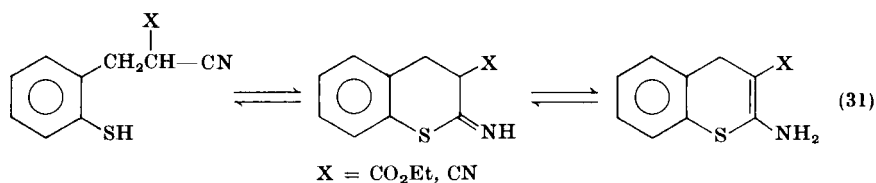
²⁶⁹ H. Zinnes and N. Lindo, German Patent 2,226,298; *Chem. Abstr.*, **78**, 124450 (1973).

²⁷⁰ T. Machiguchi, M. Hoshino, S. Ebine, and Y. Kitahara, *Chem. Commun.*, 196 (1973).

²⁷¹ A. Lüttringhaus, N. Englehard, and A. Kolb, *Justus Liebigs Ann. Chem.* **654**, 189 (1962).

²⁷² B. D. Tilak and G. T. Panse, *Indian J. Chem.* **7**, 315 (1969); *Chem. Abstr.* **71**, 21993 (1969).

reported as ring tautomers of *o*-mercaptohydrocinnamonitriles [Eq. (31)].²⁷³

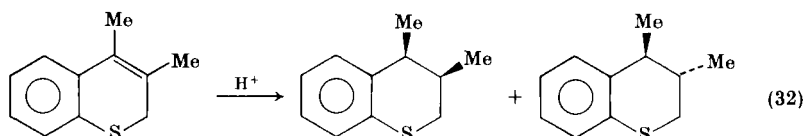


C. PREPARATION OF 1*H*-2-BENZOTHIOPYRANS

The usual synthetic entry into this ring system (**6**) is by the dehydration of isothiochromanols.²⁷⁴ Compounds **6** are also available via the photochemical reaction of thiobenzophenone with acetylenic compounds.²⁷⁵

D. REACTIONS OF 2*H*-1-BENZOTHIOPYRANS

2*H*-1-Benzothiopyrans with catalytic amounts of acid undergo disproportionation to thiochromans and benzothiopyrylium salts. In the case of 3,4-dimethyl-2*H*-1-benzothiopyran, intermolecular hydride transfer yields an 85:15 mixture of *cis*- and *trans*-3,4-dimethylthiochroman [Eq. (32)]²⁷⁶ and the 3,4-dimethylbenzothiopyrylium ion. An intermediate bridged sulfonium ion has been suggested to be responsible for the stereochemical control of this reaction.²⁷⁶ Bromination of 2*H*-1-



benzothiopyran *S,S*-dioxide in acetic acid yields the *trans*-dibromide.²⁷⁷ Reaction of **4** with thionyl chloride followed by perchloric acid produces high yields of 1-benzothiopyrylium perchlorates²⁷⁸ (e.g., Section VI.A).

²⁷³ G. W. Stacy, D. L. Eck, and T. E. Wollner, *J. Org. Chem.* **35**, 3495 (1970).

²⁷⁴ C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.* **85**, 2278 (1963).

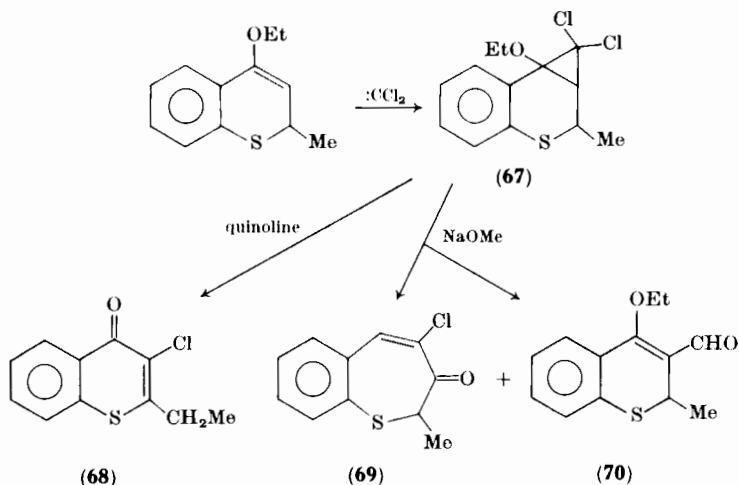
²⁷⁵ A. Ohno, T. Koizumi, Y. Ohnishi, and G. Tsuchihashi, *Tetrahedron Lett.*, 2025 (1970).

²⁷⁶ B. D. Tilak, R. B. Mitra, and Z. Muljani, *Tetrahedron* **25**, 1939 (1969).

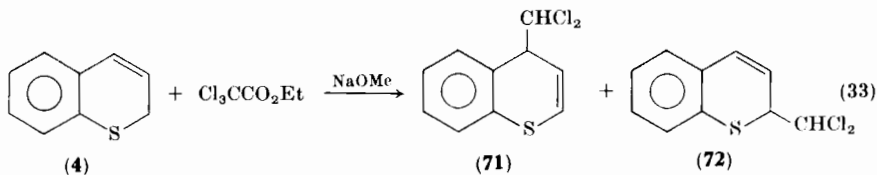
²⁷⁷ G. Pagani, S. Maiorana, and S. Bradamante, *Chim. Ind. (Milan)* **53**, 363 (1971), *Chem. Abstr.* **75**, 87999 (1971).

²⁷⁸ A. I. Tolmachev and V. P. Sribnaya, *Zh. Obshch. Khim.* **33**, 3864 (1963); *Chem. Abstr.* **75**, 13351 (1964).

4-Ethoxy-2*H*-1-benzothiopyran with dichlorocarbene yields the dichlorocyclopropane (**67**),^{279,280} which in the presence of hot quinoline²⁷⁹ produces the thiochromone (**68**), or with methoxide²⁸⁰ forms the ring-expanded benzo[*b*]thiepin (**69**) and 2*H*-1-benzothiopyran (**70**), as in Scheme 13. Reaction of dichlorocarbene with the simple 2*H*-1-benzothiopyran (**4**) produces²⁸¹ the dichloromethyl derivatives (**71**) and (**72**) of Eq. (33).



SCHEME 13



Considerable work has been carried out on the aromatic character of the 2-anion (**73**).²⁸² The *S,S*-dioxide of 2*H*-1-benzothiopyran adds diazomethane to yield **74** which is converted into **75** upon bromination/dehydrobromination.²⁸³ Compound **75** also results from the hydrogen

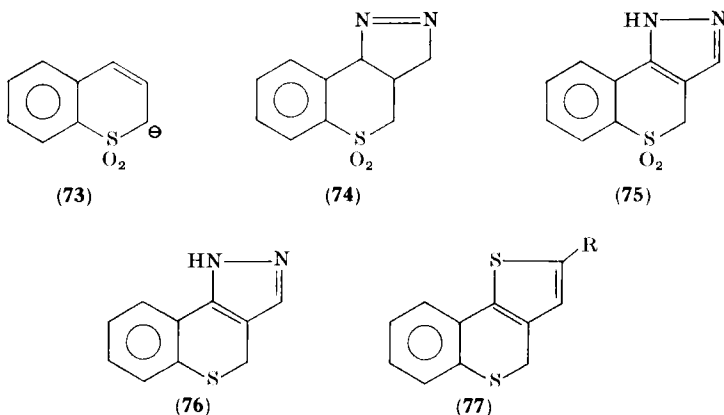
²⁷⁹ W. E. Parham and M. D. Bhavsar, *J. Org. Chem.* **29**, 1575 (1964).

²⁸⁰ W. E. Parham and D. G. Weetman, *J. Org. Chem.* **34**, 56 (1969).

²⁸¹ W. E. Parham and R. Koncos, *J. Amer. Chem. Soc.* **83**, 4034 (1961).

²⁸² S. Bradamante, S. Maiorana, A. Mangia, and G. Pagani, *J. Chem. Soc. B*, **74** (1971).

²⁸³ G. Pagani and S. Maiorana, *Chim. Ind. (Milan)* **53**, 469 (1971); *Chem. Abstr.* **75**, 48829 (1971).



peroxide oxidation of **76**, itself obtainable from 3-formylthiochroman-4-one and hydrazine.²⁸³ Compound **64** affords heterocyclic compounds, of which structure **77** is a typical example.²⁸⁴

E. REACTIONS OF 4*H*-1-BENZOTHIOPYRANS

These reactions are virtually limited to molecules possessing an ylidene functionality at the 4-carbon, formally derived from thiochromone condensations with active methylene compounds (e.g., see Section III,B).^{194,195,285}

F. REACTIONS OF 1*H*-2-BENZOTHIOPYRANS

Hydrogenation of 1,4-dimethyl-1*H*-2-benzothiopyran produces, as expected, *cis*-1,4-dimethylisothiochroman, the *S,S*-dioxide of which exists in the boat conformation.²⁶⁰ As with 2*H*-1-benzothiopyran, the anion formed from the *S,S*-dioxide of **6** shows considerable delocalization and potential aromaticity.²⁸⁶ Treatment of 1-substituted 1*H*-2-benzothiopyrans with thionyl chloride followed by perchloric acid yields 1-substituted 2-benzothiopyrylium salts,²⁸⁷ and Raney nickel desulfurization produces indane structures.^{288,289} Finally, the enamine

²⁸⁴ A. Ricci, D. Balucani, C. Rossi, and A. Croisy, *Boll. Sci. Fac. Chim. Ind. Bologna* **27**, 279 (1969); *Chem. Abstr.* **70**, 111328 (1970).

²⁸⁵ J. A. VanAllan, C. C. Petropoulos, G. A. Reynolds, and D. P. Maier, *J. Heterocycl. Chem.* **7**, 1368 (1970).

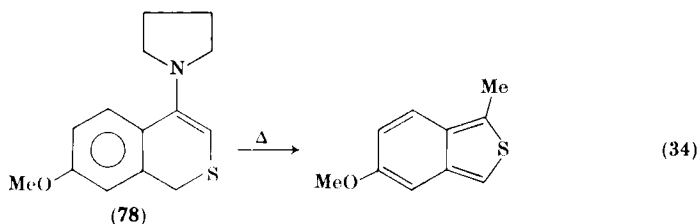
²⁸⁶ S. Bradamante, A. Mangia, and G. Pagani, *J. Chem. Soc. B*, 545 (1971).

²⁸⁷ C. C. Price and D. M. Follweiler, *J. Org. Chem.* **34**, 3302 (1969).

²⁸⁸ D. J. Dijkman and G. T. Newbold, *J. Chem. Soc.*, 13 (1952).

²⁸⁹ J. J. Brown and G. T. Newbold, *J. Chem. Soc.*, 4397 (1952).

(78) provides an unusual route to benzo[*c*]thiophenes, as in Eq. (34).²⁹⁰

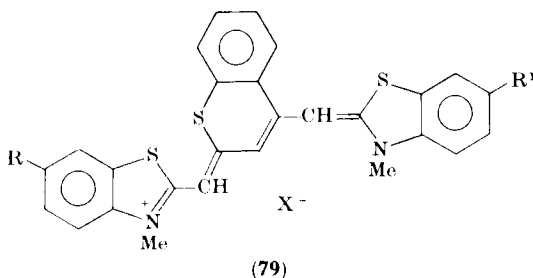


G. PHYSICOCHEMICAL PROPERTIES OF BENZOTHIOPYRANS

Ultraviolet spectra,^{291,292} dipole moments,²⁹¹ quantum chemical analysis,^{293,294} and photochromism²⁹⁵ have been reported.

H. USES OF BENZOTHIOPYRANS

Cyanine and polymethine benzothiopyran dyes (e.g., 79) have been prepared.²⁹⁶⁻²⁹⁸ The polymethine dyes are particularly stable to heat and to light, possess high infrared absorption coefficients, and have



²⁹⁰ W. N. Speekamp, F. H. M. Deckers, and H. Huisman, *J. Chem. Soc. D*, 1521 (1970).

²⁹¹ E. N. Kharlamova, E. N. Gur'yanova, and V. G. Kharchenko, *Zh. Strukt. Khim.* **12**, 637 (1971); *Chem. Abstr.* **75**, 156448 (1971).

²⁹² J. Fabian and G. Laban, *Tetrahedron* **25**, 1441 (1969).

²⁹³ L. Lunazzi and F. Taddei, *J. Mol. Spectrosc.* **25**, 113 (1968).

²⁹⁴ L. Lunazzi and F. Taddei, *Corsi Semin. Chim.*, 88 (1968); *Chem. Abstr.* **71**, 69937 (1969).

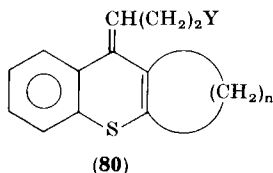
²⁹⁵ R. S. Becker and J. Kolc, *J. Phys. Chem.* **72**, 997 (1968).

²⁹⁶ G. A. Reynolds, J. A. VanAllan, J. W. Ammons, and P. B. Mauer, French Patent 1,502,822; *Chem. Abstr.* **70**, 12669 (1969).

²⁹⁷ A. I. Tolmachev and E. F. Karahan, *Ukr. Khim. Zh.* **36**, 478 (1970); *Chem. Abstr.* **73**, 131951 (1970).

²⁹⁸ B. D. Tilak and G. T. Panse, *Indian J. Chem.* **7**, 311 (1969); *Chem. Abstr.* **71**, 22888 (1969).

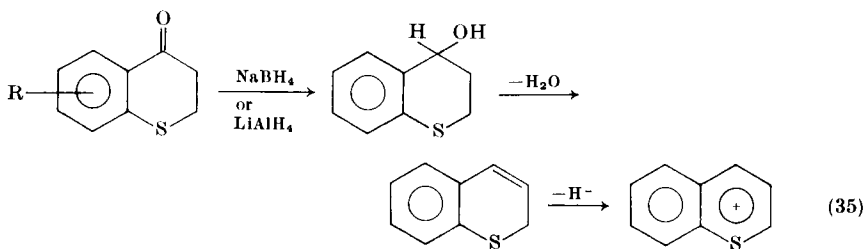
found use in "Q-switching" of lasers.²⁹⁶ Benzothiopyrans may possess insecticidal properties²⁹⁹ and be useful as psychotropic agents^{300,301} of general structure **80**.



VI. Benzothiopyrylium Salts

A. PREPARATION OF BENZOTHIOPYRYLIUM SALTS

The 1-benzothiopyrylium salts are best prepared from the easily accessible thiochroman-4-one [Eq. (35)].^{6,51,52,302-304} The common dehydrating agents include potassium hydrogen sulfate⁶ and phosphorus pentoxide^{51,302-304} while sulfuric acid/perchloric acid^{51,302-304} and trityl perchlorate⁶ have been useful as hydride extractors. Another method involves the cyclization of β -ketosulfides (e.g., **81**) or β -arythioacroleins (**82**) with perchloric acid [Eq. (36)].^{305,306}



²⁹⁹ H. C. Patel, *Diss. Abstr. B* **30**, 5434 (1970).

³⁰⁰ T. Tsujikawa, K. Tsukamura, Y. Nagawa, and Y. Saji, Japan Patent 7,304,471; *Chem. Abstr.* **78**, 111131 (1973).

³⁰¹ T. Tsujikawa, K. Tsukamura, Y. Nagawa, and Y. Saji, Japan Patent 7,328,472; *Chem. Abstr.* **78**, 159428 (1973).

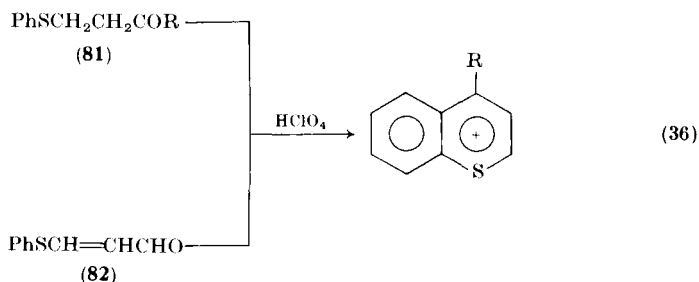
³⁰² A. Lüttringhaus and N. Engelhard, *Naturwissenschaften* **44**, 584 (1957).

³⁰³ A. Lüttringhaus and N. Engelhard, *Chem. Ber.* **93**, 1525 (1960).

³⁰⁴ T. Hashimoto, K. Kanai, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi* **86**, 438 (1965); *Chem. Abstr.* **63**, 11497 (1965).

³⁰⁵ B. D. Tilak and G. T. Panse, *Indian J. Chem.* **1**, 191 (1969).

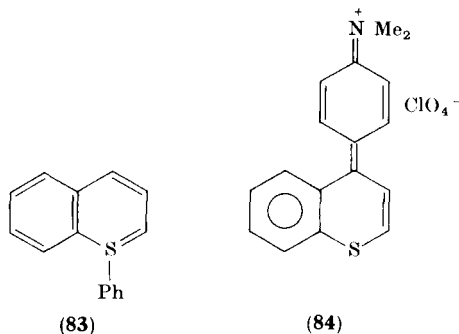
³⁰⁶ N. Engelhard and A. Kolb, *Justus Liebigs Ann. Chem.* **673**, 137 (1964).



Similarly to Eq. (35) for the 1-benzo series, 2-benzothiopyrylium salts are available from isothiochromanone.^{276,303,304}

B. REACTIONS OF BENZOTHIOPYRYLIUM SALTS

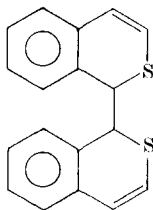
1-Benzothiopyrylium salts with nucleophilic agents yield 2*H*-1- and 4*H*-1-benzothiopyrans,³⁰⁷ while phenyllithium gives 1-thianaphthalenes³⁰⁸ (**83**) which, according to NMR spectra and dipole moments, are believed to be highly conjugated. 1-Benzothiopyrylium salts (**7**)



react with aromatic amines³⁰³ forming **84**, are oxidized³⁰⁹ to thiocromones, thiocoumarins, and benzo[*b*]thiophenes with manganese dioxide, and condense with compounds possessing an active methylene or methyl group to yield dyes.^{310–313}

- ³⁰⁷ A. Lüttringhaus, N. Engelhard and A. Kolb, *Justus Liebigs Ann. Chem.* **654**, 189 (1962).
³⁰⁸ C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.* **85**, 2278 (1963).
³⁰⁹ I. Degani and R. Fochi, *Ann. Chim. (Milan)* **58**, 251 (1968).
³¹⁰ A. I. Kiprianov and A. I. Tolmachev, *Zh. Obshch. Khim.* **30**, 638 (1960); *Chem. Abstr.* **54**, 24703 (1960).
³¹¹ A. I. Tolmachev and V. P. Stribnaya, *Zh. Obshch. Khim.* **32**, 383 (1962); *Chem. Abstr.* **58**, 1446 (1963).
³¹² B. D. Tilak and S. K. Jain, *Indian J. Chem.* **7**, 17 (1968).
³¹³ G. A. Reynolds and J. A. VanAllan, *J. Heterocycl. Chem.* **6**, 623 (1969).

Phenyllithium also converts 2-benzothiopyrylium salts to stable 2-thianaphthalenes²⁷⁴ (isomers of **83**) which possess NMR spectra resembling that of an aromatic system. Formation of 1,1'-dihydro-2,2'-dithia-1,1'-binaphthyl (**85**) is possible from the one-electron reduction of 2-benzothiopyrylium salts.³¹⁴



(85)

C. PHYSICOCHEMICAL PROPERTIES OF BENZOTHIOPYRYLIUM SALTS

Ultraviolet and NMR spectroscopic determinations are available of the pK and cationic stability of both isomeric (**7** and **8**) salts.³¹⁵⁻³¹⁸ The existence of a sulfonium sulfur in a conjugated system has been of molecular orbital interest, and some of these data have been correlated with electronic spectra.³¹⁹⁻³²² The NMR spectral data^{323,324} for both **7** and **8** have been reported, and in the former case the protons α and γ to the sulfonium center are the most deshielded. Further, the NMR indicates considerable conjugation through the sulfur in the 1-benzothiopyrylium system.³²⁴

D. USES OF BENZOTHIOPYRYLIUM SALTS

These salts have frequently been used to prepare thiocyanine

³¹⁴ C. C. Price, M. Siskin, and C. K. Miao, *J. Org. Chem.* **36**, 974 (1971).

³¹⁵ J. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 243 (1965); *Chem. Abstr.* **63**, 13050 (1965).

³¹⁶ J. Degani, R. Fochi, and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 21 (1965); *Chem. Abstr.* **63**, 8137 (1965).

³¹⁷ M. Renson and P. Pirson, *Bull. Soc. Chem. Belges* **75**, 456 (1966).

³¹⁸ J. Degani, R. Fochi, and G. Spunta, *Gazz. Chim. Ital.* **97**, 388 (1967).

³¹⁹ T. E. Young and C. J. Ohnmacht, *J. Org. Chem.* **32**, 444 (1967).

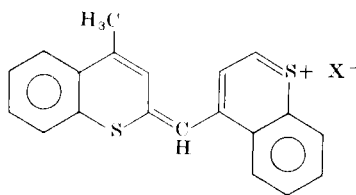
³²⁰ J. Fabian, A. Mehlhorn, and R. Zahradnik, *Theor. Chim. Acta* **12**, 247 (1968).

³²¹ J. Fabian, A. Mehlhorn, and R. Zahradnik, *J. Phys. Chem.* **72**, 3975 (1968).

³²² J. Fabian, K. Fabian, and H. Hartmann, *Theor. Chim. Acta* **15**, 319 (1969).

³²³ R. Zahradnik and J. Koutecky, *Collect. Czech. Chem. Commun.* **28**, 1117 (1963).

³²⁴ T. E. Young and C. J. Ohnmacht, *J. Org. Chem.* **32**, 1558 (1967).



(86)

dyes^{325,326} (e.g., **86**) and they have also found application as organic photoconductors³²⁷ and electrophotographic sensitizers.³²⁸

³²⁵ B. D. Tilak, *Ind. Chim. Belge* **32**, 50 (1967); *Chem. Abstr.* **70**, 79132 (1969).

³²⁶ R. Wizinger, *Experientia* **1**, 29 (1945).

³²⁷ J. A. VanAllan, French Patent 2,005,060; *Chem. Abstr.* **73**, 115065 (1970).

³²⁸ G. A. Reynolds and J. A. VanAllan, U.S. Patent 889,023; *Chem. Abstr.* **75**, 114836 (1971).

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Thioureas in the Synthesis of Heterocycles

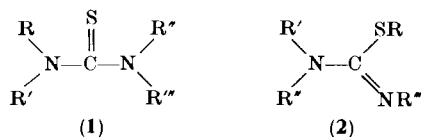
T. SCOTT GRIFFIN, THOMAS S. WOODS, AND DANIEL L. KLAYMAN

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Washington, D.C.*

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I. Introduction

Of the many reviews¹⁻⁴ dealing with the chemistry of thioureas, none is devoted exclusively to their use in the preparation of heterocyclic compounds. This chapter will present the reactions and synthetic methods involved in these preparations and will illustrate the versatility of thioureas in the formation of heterocycles. Discussion will be limited to acyclic thioureas (**1**) and thiopseudoureas (**2**) in which the adjacent atoms of the substituent R-groups may be of any element other than



nitrogen. Thus thiosemicarbazides and imidazolidine-2-thiones, for example, are excluded from consideration, but thiobiurets and thiocarbamoyl isothiocyanates are not. Selenium-containing analogs of **1** and **2** which meet the above criteria are included.

This review will not discuss the large body of literature concerning thiourea-induced sulfur insertions giving thiiranes from epoxides⁵ and from haloalcohols.⁶

In this chapter, the heterocyclic systems prepared from thioureas are presented in order of increasing ring size and in order of increasing numbers of heteroatoms. The heteroatoms have been arranged in the following sequence: nitrogen, sulfur, oxygen, other elements. Heterocycles prepared from selenoureas and selenopseudoureas are presented together with their sulfur analogs. Heteropolycycles are discussed in a separate section and are grouped according to general ring type, rather than strictly by ring size.

II. Four-Membered Rings

Thioureas are useful in the preparation of two four-membered ring systems: thietanes and 1,3-thiazetidin-4-ones. Thietanes (**3**) can be

¹ D. C. Schroeder, *Chem. Rev.* **55**, 181 (1955).

² E. G. Curphey, *Chem. Prod. Chem. News* **18**, 98 (1955).

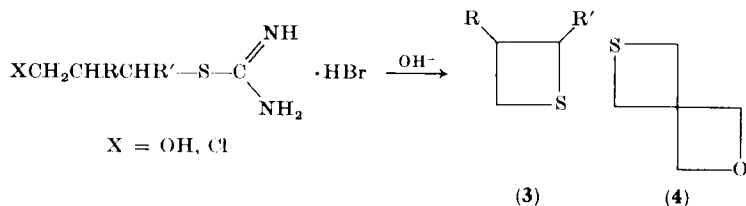
³ F. Kurzer, *Chem. Rev.* **56**, 95 (1956).

⁴ F. Kurzer, *Chem. Rev.* **50**, 1 (1952).

⁵ D. D. Reynolds and D. F. Fields, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.) Vol. 19, Pt. 1, pp. 579-581. Wiley (Interscience), New York, 1964.

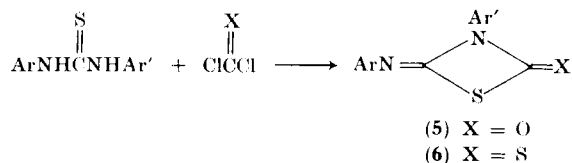
⁶ R. N. Kienle, U.S. Patent 2,766,256 (1956).

prepared by reaction of 2-(3-hydroxylalkyl)-⁶ or 2-(3-chloroalkyl)-2-thiopseudourea hydrobromides⁷ with base. The latter reaction has been reviewed by Etienne *et al.*⁷



Campbell⁸ indicated that 2-oxa-6-thiaspiro[3.3]heptane (4) was formed from 3,3-bis(chloromethyl)oxetane and thiourea; however, no experimental details were given.

The reaction between 1,3-diaryl-2-thioureas and phosgene or thio-phosgene has been reported to yield 2-arylimino-3-aryl-1,3-thiazetidin-4-ones (5)⁹ or thiones (6).¹⁰ Recent studies on the reaction between



1-methyl or 1-*p*-toluenesulfonyl-2-thioureas and phosgene suggested that the former must also be aryl-substituted at the 3-position in order to form the cyclic derivatives.¹¹

Fromm¹² proposed that 1,3-diazetidines-2-thiones were the products of the reaction between dithiobiurets and aldehydes or ketones, which he called aldurets and keturets, respectively. These structures were subsequently shown to be hexahydrotriazines by Fairfull and Peak.¹³ Kurzer,³ in his review of dithiobiurets, summarized the structural work on aldurets and keturets. Dixon and Taylor¹⁴ claimed that 1,3-diazetidines-2-thiones were the products of the acid-catalyzed treatment of

⁷ Y. Etienne, R. Soulas, and H. Lumbroso, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 19, Pt. 2, pp. 684–685. Wiley (Interscience), New York, 1964.

⁸ T. W. Campbell, *J. Org. Chem.* **22**, 1029 (1957).

⁹ W. Will, *Ber.* **14**, 1485 (1881).

¹⁰ M. Freund and H. Wolf, *Ber.* **25**, 1456 (1892).

¹¹ H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron* **22**, 1565 (1966).

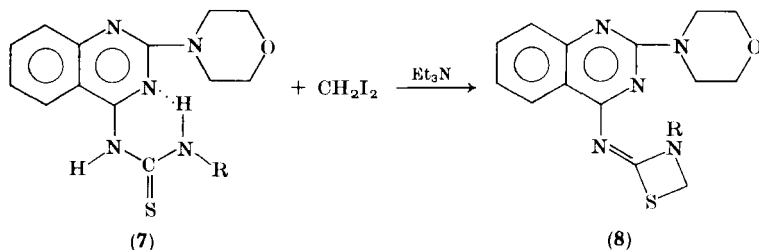
¹² E. Fromm, *Justus Liebigs Ann. Chem.* **275**, 20 (1893).

¹³ A. E. S. Fairfull and D. A. Peak, *J. Chem. Soc.*, 803 (1955).

¹⁴ A. E. Dixon and J. Taylor, *J. Chem. Soc.* **109**, 1244 (1916).

thioureas with aldehydes. However, this work has not been confirmed, and reactions between thioureas and aldehydes usually yield hexahydrotriazines (see Section IV, A, 3).

Foerster¹⁵ reported that 2-phenylimino-3-phenyl-1,3-thiazetidine was formed by reaction of 1,3-diphenyl-2-thiourea with methylene iodide. Underwood and Dains¹⁶ repeated this reaction and obtained only a gummy product; however, they obtained crystalline 1,3-thiazetidines from 1,3-di-*p*-tolyl-2-thiourea and also from 1,5-diphenyl-2-methyl-2,4-dithiopseudobiuret. Recently, Ried *et al.*¹⁷ observed the formation in low yields of 1,3-thiazetidines from unsymmetrically disubstituted thioureas in the presence of triethylamine. They reported that 1-(4-quinazolyl)-2-thioureas (7), which have an intramolecular hydrogen bond, react rapidly with methylene iodide in the presence of triethylamine to give the 1,3-thiazetidines (8) in high yields.¹⁷



III. Five-Membered Rings

A. NITROGEN-CONTAINING RINGS

1. Two Nitrogen Atoms

Formation of imidazoles from thiourea derivatives has been limited largely to the 2-alkylthio or 2-aralkylthio-substituted rings (unsubstituted 2-mercaptoimidazoles will be classified as 4-imidazoline-2-thiones in this review).

For example, the reaction of thiopseudoureas with phenacyl bromide was reported to yield **9**.^{18,19} Gompper *et al.*²⁰ were able to prepare 4-amino-5-cyano-1-methyl-2-methylthioimidazole (**11**) in nearly quantitative yield via ethoxide-promoted cyclization of **10**.

¹⁵ F. Foerster, *Ber.* **21**, 1857 (1888).

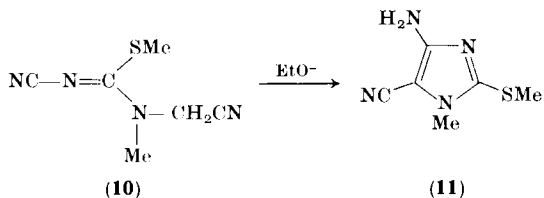
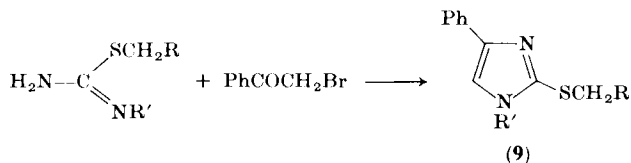
¹⁶ H. G. Underwood and F. B. Dains, *J. Amer. Chem. Soc.* **57**, 1769 (1935).

¹⁷ W. Ried, W. Merkel and O. Möisinger, *Justus Liebigs Ann. Chem.* **1362** (1973).

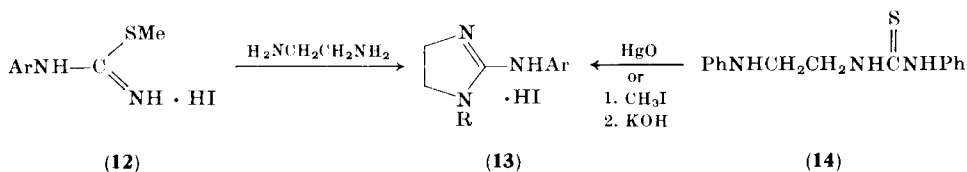
¹⁸ R. M. Dodson, *J. Amer. Chem. Soc.* **70**, 2753 (1948).

¹⁹ R. M. Dodson and F. Ross, *J. Amer. Chem. Soc.* **72**, 1478 (1950).

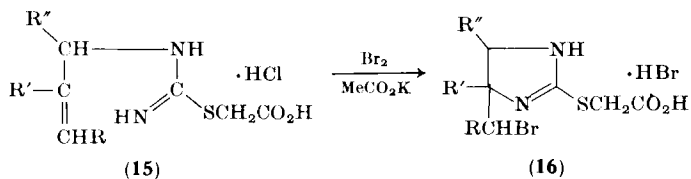
²⁰ R. Gompper, M. Gäng, and F. Saygin, *Tetrahedron Lett.*, 1885 (1966).



Substituted 2-amino-2-imidazolines (**13**, R = H) may be prepared by a useful general method developed by Bloom²¹ by the reaction of thiopseudourea hydriodides (**12**) with ethylenediamine. Another



procedure was reported by Adcock and Lawson,²² who cyclized 1-phenyl-3-(2-phenylaminoethyl)-2-thiourea (**14**), either directly with mercuric oxide or indirectly by treating **14** with iodomethane to form the corresponding *S*-methiodide, which was in turn cyclized to **13** (Ar = R = Ph) by the action of base. Also Krasnitskaya *et al.*²³ were able to generate 2-alkylthio-2-imidazolines (**16**) by reaction of unsaturated side-chain thiopseudoureas (**15**) with bromine and potassium acetate.

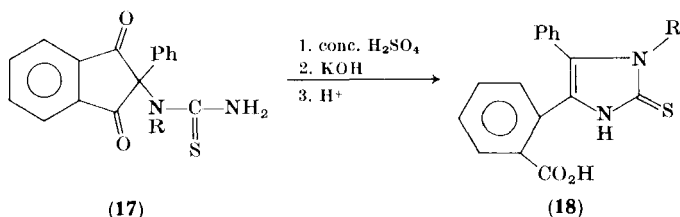


²¹ B. M. Bloom, U.S. Patent 2,899,426 (1959); *Chem. Abstr.* **54**, 588 (1960).

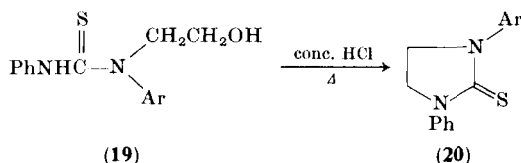
²² B. Adcock and A. Lawson, *J. Chem. Soc.*, 474 (1965).

²³ T. A. Krasnitskaya, I. V. Smolanka, and A. L. Vais, *Khim. Geterotsikl. Soedin.*, 424 (1973).

The two general methods for preparation of 4-imidazoline-2-thiones are the reaction of acyloins with thioureas²⁴⁻²⁶ and the acid hydrolysis of alkyl- or arylthiureidoacetals.^{27,28} The above reactions have been summarized in a review by Hofmann.²⁹ Aren and Bite³⁰ recently reported that the 2-phenyl-2-thiureido-1,3-indanediones (**17**) undergo rearrangement in strong acid to produce in high yield a series of 4-imidazoline-2-thiones (**18**).



Unsubstituted imidazolidine-2-thione, also known as ethylene thiourea, was one of the reported products (along with aniline, 2-anilino-2-imidazoline, and hydrogen sulfide) which resulted from thermolysis of 1-(2-aminoethyl)-3-phenyl-2-thiourea.³¹ Cherbuliez *et al.*³² found that 1,3-diarylimidazolidine-2-thiones (**20**) were formed by treatment of the 1,3-diaryl-1-(2-hydroxyethyl)-2-thioureas (**19**) with concentrated hydrochloric acid.



Imidazolidin-4-one-2-thiones (**21**; R = H) are commonly known as thiohydantoins and the isomeric 2-iminothiazolidin-4-ones (**22**; R = H) have been frequently referred to as pseudothiohydantoins. In earlier

²⁴ R. Anschütz and K. Schwickerath, *Justus Liebigs Ann. Chem.* **284**, 9 (1895).

²⁵ A. Basse and H. Klinger, *Ber.* **31**, 1217 (1898).

²⁶ H. Müller, *Justus Liebigs Ann. Chem.* **284**, 25 (1895).

²⁷ W. Marckwald, *Ber.* **25**, 2354 (1892).

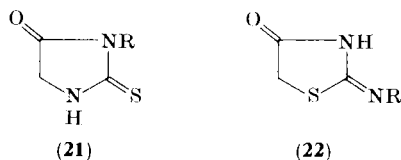
²⁸ A. Wohl and W. Marckwald, *Ber.* **22**, 568 (1889).

²⁹ K. Hofmann, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 6, pp. 77-82. Wiley (Interscience), New York, 1953.

³⁰ A. K. Aren and Dz. V. Bite, *Khim. Geterotsikl. Soedin.*, 329 (1968).

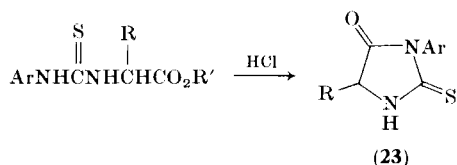
³¹ L. Helgen, O. Stoutland, and C. L. Agre, *J. Org. Chem.* **24**, 884 (1959).

³² E. Cherbuliez, B. Willhalm, S. Jaccard, and J. Rabinowitz, *Helv. Chim. Acta* **50**, 2563 (1967).



literature (1877–1879) there occurred the assignment of structure **21** to products of reactions between thiourea and chloroacetic acid³³ or α -chloropropionic anhydride³⁴ when, in fact, the products had structure **22**. This subject has been discussed in a general review of hydantoin by Ware.³⁵ However, recently Achary and Nayak³⁶ showed that 1-(2-pyridyl)-2-thiourea produced a pseudothiohydantoin (**22**; R = 2-pyridyl) when treated with chloroacetic acid in ethanol in the presence of sodium acetate, and a thiohydantoin (**21**; R = 2-pyridyl) when the reaction was performed in pyridine.

General methods for preparation of imidazolidin-4-one-2-thiones include the reaction of thioureas with α -dicarbonyl compounds,^{37,38} with ethyl phenylpropiolate,³⁹ and with phenyl chlorothiolacetate,⁴⁰ and cyclization in acid of 1-(carbethoxymethyl)-2-thioureas.⁴¹ The analogous reaction of α -dicarbonyl compounds with selenoureas produce imidazolidin-4-one-2-selones.⁴² Berlin and Levi⁴³ utilized the acid-catalyzed cyclization of 1-aryl-3-carbalkoxymethyl-2-thioureas to produce 3-arylimidazolidin-4-one-2-thiones (**23**).



³³ P. Claesson, *Ber.* **10**, 1346 (1877).

³⁴ B. Freytag, *J. Prakt. Chem.* **20**, 380 (1879).

³⁵ E. Ware, *Chem. Rev.* **46**, 403 (1950).

³⁶ T. E. Achary and A. Nayak, *Curr. Sci.* **41**, 539 (1972); *Chem. Abstr.* **77**, 114305 (1972).

³⁷ H. Biltz, *Ber.* **42**, 1792 (1909).

³⁸ B. Sjollesma and L. Seekles, *Rec. Trav. Chim.* **44**, 827 (1925); *Chem. Abstr.* **19**, 3478 (1925).

³⁹ S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.* **77**, 239 (1900).

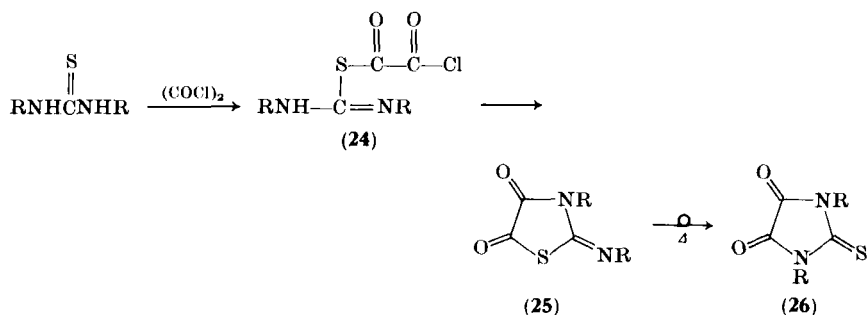
⁴⁰ C. E. Dalglish and F. G. Mann, *J. Chem. Soc.*, 559 (1947).

⁴¹ T. B. Johnson and A. G. Renfrew, *J. Amer. Chem. Soc.* **47**, 240 (1925).

⁴² P. Bergmann, F. Pragst, and H. Paul, *Arch. Pharm. (Weinheim)* **299**, 499 (1966).

⁴³ A. Ya. Berlin and I. S. Levi, *Zh. Obshch. Khim.* **33**, 860 (1963).

Imidazolidine-4,5-dione-2-thiones (**26**), also known as thioparabanic acids, can be prepared by heating thioureas with oxalyl chloride^{44,45} or diethyl oxalate.^{46,47} Cyanogen may also be used if the reactants are heated in the presence of acid.⁴⁸ Stoffel⁴⁵ and Ulrich and Sayigh⁴⁹ have studied in detail the reaction of thioureas with oxalyl chloride and were able to isolate intermediate thiazolidine-4,5-diones (**25**) which on heating rearranged to the imidazolidine-4,5-dione-2-thiones (**26**). Thus, in the mechanism proposed by Stoffel,⁴⁵ initial attack of the oxalyl chloride is on sulfur to form **24**, which can cyclize to **25**. Further heating then causes rearrangement of **25** to **26**.



2. Three Nitrogen Atoms

3,5-Diamino-1,2,4-triazoles (**29**) are readily formed by reaction of 2,4-dimethyl-(or diethyl)-2,4-dithiopseudobiurets (**27**) with hydrazine hydrate^{50,51} or aryl hydrazines.⁵² 1-Aryl-3-cyano-2-methyl-2-thiopseudoureas (**28**), which result from acid treatment of **27** (R = aryl, R' = H), also react with hydrazine to form **29**.⁵¹ When treated with hydrazine, dithiobiurets were reported to produce mixtures consisting of 3,5-diamino-1,2,4-triazoles and 3-arylamino-5-mercapto-1,2,4-tri-

⁴⁴ H. Biltz and E. Topp, *Ber.* **46**, 1387 (1913).

⁴⁵ P. J. Stoffel, *J. Org. Chem.* **29**, 2794 (1964).

⁴⁶ M. Nencki, *Ber.* **7**, 779 (1874).

⁴⁷ A. Michael, *J. Prakt. Chem.* **49**, 26 (1894).

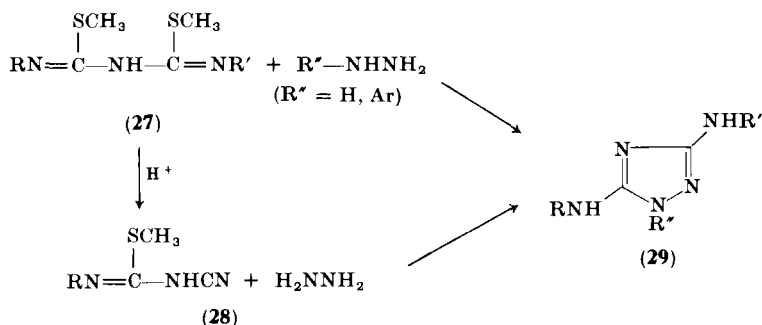
⁴⁸ T. Andreasch, *Monatsh. Chem.* **2**, 277 (1881).

⁴⁹ H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.* **30**, 2781 (1965).

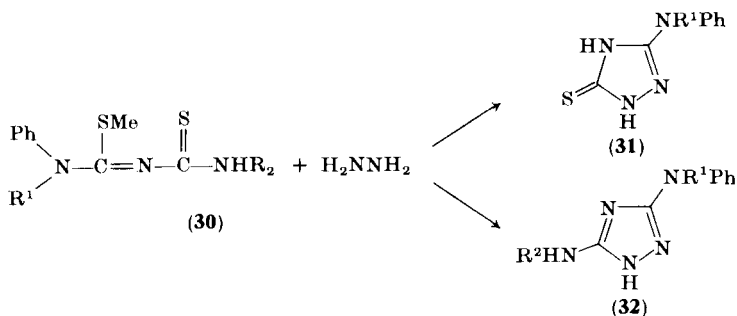
⁵⁰ F. H. S. Curd, D. G. Davey, D. N. Richardson, and R. de B. Ashworth, *J. Chem. Soc.*, 1739 (1949).

⁵¹ J. S. Davidson, *J. Chem. Soc. C*, 194 (1969).

⁵² H. G. Underwood and F. B. Dains, *Univ. Kansas Sci. Bull.* **24**, 5 (1936); *Chem. Abstr.* **32**, 3399 (1938).



azoles.^{53,54} Davidson^{51,55} and Werbel *et al.*⁵⁶ were able to obtain 3-arylamino-5-amino-1,2,4-triazoles exclusively by the reaction of 1-aryl-4-methyl-2,4-dithiopseudobiurets with hydrazine. In addition, Davidson⁵⁷ studied the hydrazinolysis of a series of 2-methyl-1-phenyl-2,4-dithiopseudobiurets (**30**; R¹, R² = alkyl or aryl) and found that the predominant products, in yields up to 90%, were the 5-mercapto-1,2,4-triazoles (**31**) when R² was aliphatic, but when R² was aromatic, mixtures of **31** and **32**, in which the latter were predominant, resulted. Hydrazinolysis of 2-benzyl-1-phenyl-3-phenylamidino-2-thiopseudourea was reported to produce 3,5-diphenylamino-1,2,4-triazole in 75% yield.⁵⁸



⁵³ F. Arndt, E. Milde, F. Tschenscher, F. Bielich, and G. Eckert, *Ber.* **55B**, 12 (1922).

⁵⁴ E. Fromm, L. Brück, R. Runkel, and E. Mayer, *Justus Liebigs Ann. Chem.* **437**, 106 (1924).

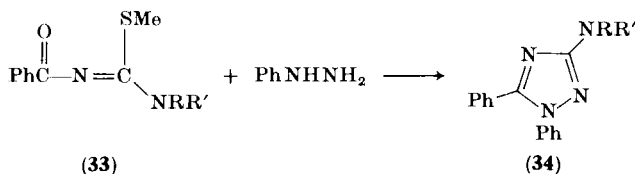
⁵⁵ J. S. Davidson, *J. Chem. Soc. C*, 2471 (1967).

⁵⁶ L. M. Werbel, E. F. Elslager, and V. P. Chu, *J. Heterocycl. Chem.* **10**, 631 (1973).

⁵⁷ J. S. Davidson, *J. Prakt. Chem.* **314**, 663 (1972).

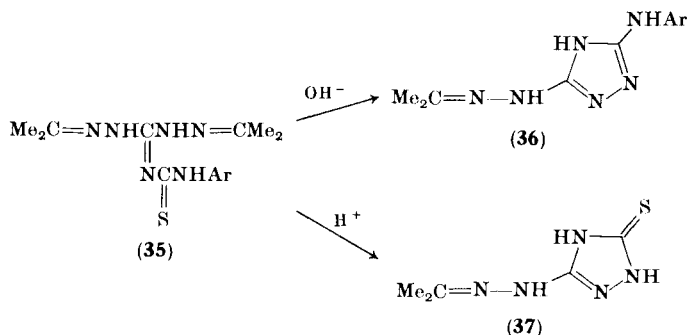
⁵⁸ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 3333 (1963).

Wheeler and Beardsley⁵⁹ were able to prepare the substituted 1,2,4-triazoles (34) by reaction of 2-methyl-1-benzoyl-2-thiopseudoureas (33) with phenyl hydrazine. Similarly, Davidson⁶⁰ treated hydrazine with



2-methyl-1,1-dibenzoyl-2-thiopseudourea to produce 3-benzamido-5-phenyl-1,2,4-triazole in 85% yield. If 1-benzoyl-2-thioureas, rather than benzoyl-2-thiopseudoureas, are treated with hydrazines, the products are 3-mercapto-1,2,4-triazoles as well as 3-amino-1,2,4-triazoles.⁶¹ A variety of 3-amino-1,2,4-triazoles have also been prepared in moderately good yields via the reaction of hydrazides with thiopseudoureas.^{62,63}

The intermediate *N*-anilinoamidino-2-thioureas, which result from the treatment of 3,5-diimino-1,2,4-dithiazolines (thiurets) with phenylhydrazine, were reported by Fromm⁶⁴⁻⁶⁶ to cyclize to 3,5-diamino-1,2,4-triazoles. Kurzer and co-workers, who had earlier reported the cyclization of amidinothioureas to 1,2,4-triazoles,⁶⁷ extended this work to 1,3-bis(isopropylideneimino)-2-arylthiocarbamoylguanidines (35),



⁵⁹ H. L. Wheeler and A. P. Beardsley, *Amer. Chem. J.* **29**, 73 (1903).

⁶⁰ J. S. Davidson, *Chem. Ind. (London)*, 464 (1972).

⁶¹ R. Sgarbi, *Chim. Ind. (Milan)* **48**, 18 (1966).

⁶² K. Biemann and H. Bretschneider, *Monatsh. Chem.* **89**, 604 (1958).

⁶³ E. Hoggarth, *J. Chem. Soc.*, 612 (1950).

⁶⁴ E. Fromm and E. Vettor, *Justus Liebigs Ann. Chem.* **356**, 178 (1907).

⁶⁵ E. Fromm and A. Weller, *Justus Liebigs Ann. Chem.* **361**, 302 (1908).

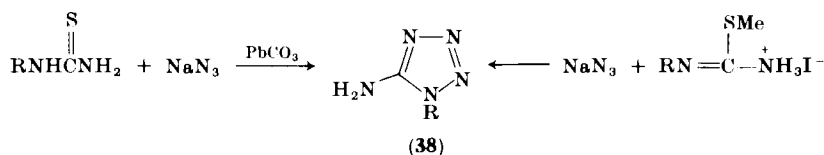
⁶⁶ E. Fromm, *Justus Liebigs Ann. Chem.* **394**, 258 (1912).

⁶⁷ L. E. A. Godfrey and F. Kurzer, *J. Chem. Soc.*, 3437 (1960).

which they found would cyclize to 3-arylamino-5-hydrazono-1,2,4-triazoles (36) in base and to 3-hydrazono-5-mercapto-1,2,4-triazoles (37) in acid.⁶⁸

3. Four Nitrogen Atoms

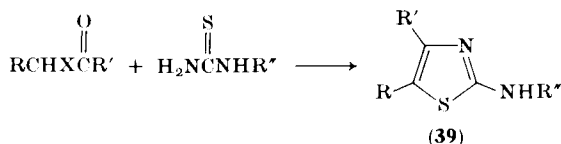
1-Alkyl (or aryl) 5-aminotetrazoles (38) can be prepared either from thioureas by reaction with sodium azide in the presence of lead carbonate⁶⁹ or from 2-thiopseudourea hydriodides by reaction with sodium azide.⁷⁰



B. NITROGEN- AND SULFUR-CONTAINING RINGS

1. One Nitrogen Atom and One Sulfur Atom

The reaction between thioureas and α -halo ketones or aldehydes to form 2-aminothiazoles (39), first developed by Hantzsch⁷¹ and Traumann,^{71,72} is one of the oldest and most important uses for thioureas in



the synthesis of heterocycles. When the thioureas are 1,3-disubstituted, the products are substituted 2-amino-4-thiazolines.⁷² The α -halo ketones have also been replaced by α -diazo ketones⁷³ and by α,β -epoxy ketones.⁷⁴ A thorough discussion of the above reactions, including

⁶⁸ F. Kurzer and K. Douraghi-Zadeh, *J. Chem. Soc.*, 4448 (1965).

⁶⁹ R. Stollé, K. Ehrmann, D. Rieder, H. Wille, H. Winter, and F. Henke-Stark, *J. Prakt. Chem.* **134**, 282 (1932).

⁷⁰ W. L. Garbrecht and R. M. Herbst, *J. Org. Chem.* **18**, 1022 (1953).

⁷¹ A. Hantzsch and V. Traumann, *Ber.* **21**, 938 (1888).

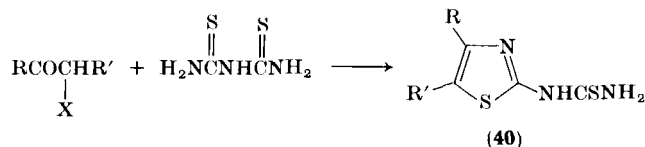
⁷² V. Traumann, *Justus Liebigs Ann. Chem.* **249**, 31 (1888).

⁷³ L. C. King and F. M. Miller, *J. Amer. Chem. Soc.* **71**, 367 (1949).

⁷⁴ C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson, and W. E. Savige, *J. Chem. Soc.*, 2573 (1949).

methods for *in situ* generation of the reactive carbonyl compound, is contained in the general review of thiazoles by Sprague and Land⁷⁵ which appeared in 1957. Numerous papers have appeared since 1957 on the use of the above type reaction to prepare 2-aminothiazole derivatives for medicinal testing. The analogous reaction of α -halo aldehydes or ketones with selenoureas to produce 2-aminoselenazoles has been reviewed by Bulka^{76,77} and Shine.⁷⁸

Dithiobiurets react with α -halo ketones⁷⁹⁻⁸² or aldehydes (generated *in situ*)⁸³ to yield 2-thiureidothiazoles (**40**), which can be converted in two steps to 2-guanidinothiazoles.⁸¹ However, Beyer and Hantschel⁸⁴ found that 2-guanidinothiazoles could be more conveniently prepared via the reaction of 1-amidino-2-thiourea with α -halo ketones or aldehydes.



Bartoszewski and Jerzmanowska⁸⁵ found that mixtures of isomeric thiazolines were frequently produced by the reaction of various aryl-substituted unsymmetrical thioureas with chloroacetone. However, Murav'eva and Shchukina^{86,87} observed that treatment of 1-aryl-3-

⁷⁵ J. M. Sprague and A. H. Land, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, pp. 484-723. Wiley, New York, 1957.

⁷⁶ E. Bulka, *Advan. Heterocycl. Chem.* **2**, 343 (1963).

⁷⁷ E. Bulka, in "Organic Selenium Compounds: Their Chemistry and Biology" (D. L. Klayman and W. H. H. Günther, eds.), pp. 459-496. Wiley, New York, 1973.

⁷⁸ R. J. Shine, in "Organic Selenium Compounds: Their Chemistry and Biology" (D. L. Klayman and W. H. H. Günther, eds.), pp. 284-288. Wiley, New York, 1973.

⁷⁹ E. Fromm and E. Philippe, *Ber.* **32**, 835 (1899).

⁸⁰ R. L. Sperry, U.S. Patent 2,470,585 (1949); *Chem. Abstr.* **43**, 5425 (1949).

⁸¹ R. L. McKee and J. D. Thayer, *J. Org. Chem.* **17**, 1494 (1952).

⁸² H. Beyer and K. Pommerening, *Chem. Ber.* **99**, 2931 (1966).

⁸³ I. Iwataki, *Bull. Chem. Soc. Jap.* **45**, 3218 (1972).

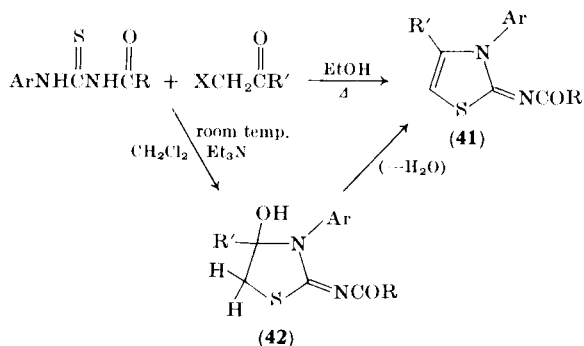
⁸⁴ H. Beyer and H. Hantschel, *Chem. Ber.* **95**, 893 (1962).

⁸⁵ J. Bartoszewski and Z. Jerzmanowska, *Rocz. Chem.* **37**, 11 (1963); *Chem. Abstr.* **59**, 7510 (1963).

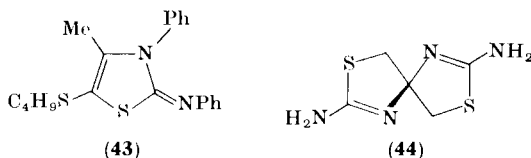
⁸⁶ K. M. Murav'eva and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 2327 (1960); *Chem. Abstr.* **55**, 9376 (1961).

⁸⁷ K. M. Murav'eva and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 2334 (1960); *Chem. Abstr.* **55**, 9376 (1961).

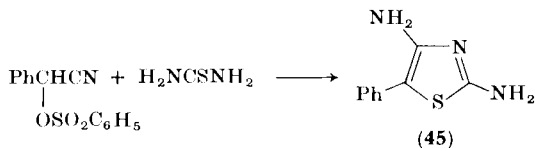
acyl-2-thioureas with α -halo ketones yielded only the thiazoline isomer **41** with the acyl substituent on the exocyclic nitrogen. These authors also isolated the intermediate 4-hydroxythiazolidines (**42**) using milder conditions than were used for the formation of the thiazolines.



The treatment of 1,3-diphenyl-2-thiourea with acetone in the presence of butylsulfenyl chloride was reported by Kopylova *et al.*⁸⁸ to yield the 5-butylthio-4-thiazoline (**43**; isolated as a picrate). Another interesting thiazoline is 2,2'-diamino-4,4'-spirobithiazoline (**44**) produced from fusion of 1,3-dichloroacetone and thiourea.⁸⁹



Dodson and Turner⁹⁰ were able to prepare the 2,4-diaminothiazole (**45**) by reaction of thiourea with α -cyanobenzyl benzenesulfonate. The

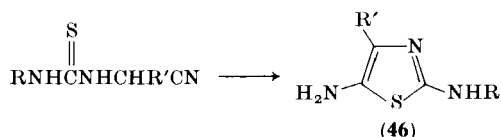


⁸⁸ B. V. Kopylova, M. N. Khasanova, R. Kh. Freydlina, *Uzb. Khim. Zh.* **29** (2) (1968); *Chem. Abstr.* **70**, 68240 (1969).

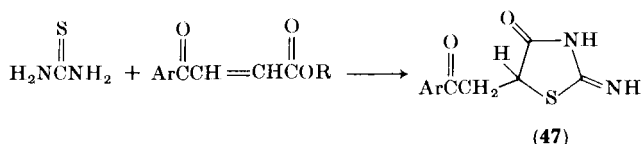
⁸⁹ J. Harley-Mason, *J. Chem. Soc.*, 323 (1947).

⁹⁰ R. M. Dodson and H. W. Turner, *J. Amer. Chem. Soc.* **73**, 4517 (1951).

reaction was further studied by Taylor *et al.*, who found that 1-phenyl-2-thiourea gave 4-amino-3,5-diphenyl-2-imino-4-thiazoline⁹¹ and 1,3-disubstituted thioureas gave the corresponding thiazolines.⁹² A useful general method for the preparation of 2,5-diaminothiazoles (**46**) is the cyclization of 1-cyanomethyl-2-thioureas.^{93,94}



Several new syntheses of thiazoles from thioureas have been developed in recent years. Werbel⁹⁵ was able to prepare 2-aminothiazoles by reaction of thioureas with bis(β -chloroethyl) ether. 1,3-Disubstituted thioureas, however, yielded disubstituted 4-thiazolines. In a German patent, Reisinger⁹⁶ reported that 2-aminothiazole was formed in 88% yield from thiourea and vinyl acetate in the presence of sulfur chloride. A method for the preparation of the 4-hydroxy-2-aminothiazole (**47**), which probably exists in the tautomer shown, has been developed by Delaby *et al.*⁹⁷ via the reaction of thiourea with β -acyl-acrylic acid or its esters. Zbiral⁹⁸ has observed that acylvinylphos-



phonium salts (**48**) will add thiourea to form thiopseudoureas which can cyclize to 2-aminothiazolylmethylphosphonium salts (**49**). The tri-

⁹¹ E. C. Taylor, Jr., J. Wolinsky, and H.-H. Lee, *J. Amer. Chem. Soc.* **76**, 1866 (1954).

⁹² E. C. Taylor, Jr., G. A. Berchtold, N. A. Goeckner, and F. G. Stroehmann, *J. Org. Chem.* **26**, 2715 (1961).

⁹³ J. M. Balquist and F. J. Goetz, *J. Heterocycl. Chem.* **9**, 937 (1972).

⁹⁴ C. W. Capp, A. H. Cook, J. D. Downer, and I. Heilbron, *J. Chem. Soc.*, 1340 (1948).

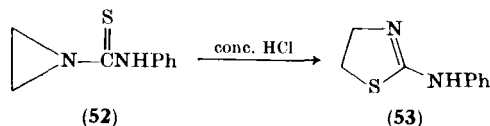
⁹⁵ L. M. Werbel, *Chem. Ind. (London)*, 1634 (1966).

⁹⁶ K. Reisinger, West German Patent 1,812,267 (1970); *Chem. Abstr.* **73**, 45498 (1970).

⁹⁷ R. Delaby, S. Danton, and P. Chabrier, *Bull. Soc. Chim. Fr.*, 2061 (1961).

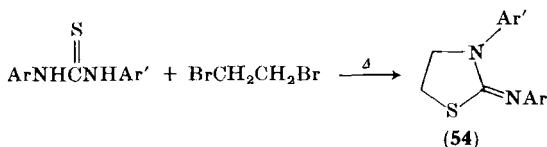
⁹⁸ E. Zbiral, *Tetrahedron Lett.*, 5107 (1970).

*et al.*¹⁰⁵⁻¹⁰⁷ found that the sulfate or phosphate esters of 1-(2-hydroxyethyl)-2-thioureas would readily cyclize with acid or base to 2-amino-2-thiazolines. In a further extension of this reaction, Deutsch and Fanta¹⁰⁸ found that the same 2-amino-2-thiazoline (**53**) produced in 90% yield by acid-catalyzed cyclization of 1-phenyl-3-(2-hydroxyethyl)-2-thiourea was also formed in 91% yield by treatment of 1-(*N*-phenylthiocarbamoyl)aziridine (**52**) with concentrated hydrochloric acid. This reaction was first reported by Gabriel and Stelzner,¹⁰⁹ who erroneously formulated the aziridine (**52**) as 1-phenyl-3-vinyl-2-thiourea. Iwakura and



Nabeya¹¹⁰ found that the same reaction occurred in acetic acid, and Heine *et al.*¹¹¹ reported that sodium iodide in acetone effectively promoted the rearrangement. Tišler¹¹² utilized this procedure to produce a variety of 2-arylamino-2-thiazolines.

In a reaction first reported by Will in 1881,⁹ 1,3-diaryl-2-thioureas heated with ethylene bromide yield 2-iminothiazolidines (**54**).^{113,114}



When Ar and Ar' were not identical, Foerster¹⁵ claimed to have isolated a single isomer of **54**. However, Dashen and Brewster¹⁰³ studied a series of substituted 1,3-diphenyl-2-thioureas in this reaction and came to the conclusion that the phenyl group with more electron-donating

¹⁰⁵ E. Cherbuliez, Br. Baehler, O. Espejo, E. Frankenfeld, and J. Rabinowitz, *Helv. Chim. Acta* **49**, 2608 (1966).

¹⁰⁶ E. Cherbuliez, H. Jindra, and J. Rabinowitz, *Helv. Chim. Acta* **49**, 1951 (1966).

¹⁰⁷ E. Cherbuliez, Br. Baehler, O. Espejo, S. Jaccard, H. Jindra, and J. Rabinowitz, *Helv. Chim. Acta* **49**, 2408 (1966).

¹⁰⁸ A. S. Deutsch and P. E. Fanta, *J. Org. Chem.* **21**, 892 (1956).

¹⁰⁹ S. Gabriel and R. Stelzner, *Ber.* **28**, 2929 (1895).

¹¹⁰ Y. Iwakura and A. Nabeya, *Nippon Kagaku Zasshi* **77**, 773 (1956); *Chem. Abstr.* **52**, 9028 (1958).

¹¹¹ H. W. Heine, W. G. Kenyon, and E. M. Johnson, *J. Amer. Chem. Soc.* **83**, 2570 (1961).

¹¹² M. Tišler, *Arch. Pharm. (Weinheim)* **291**, 457 (1958).

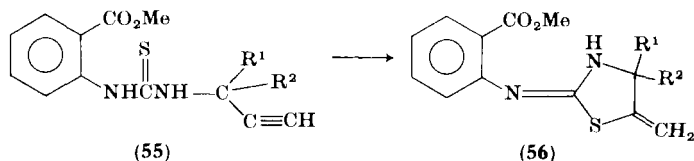
¹¹³ G. Noah, *Ber.* **23**, 2195 (1890).

¹¹⁴ H. Erlenmeyer, H. Schulthess, and H. Bloch, *Helv. Chim. Acta* **30**, 1336 (1947).

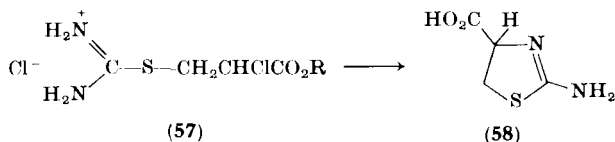
substituents would appear on the ring nitrogen in the product. Using the above reaction, Bradsher *et al.*¹¹⁵ were able to prepare a variety of benzyl-substituted 2-iminothiazolidines.

Albert¹¹⁶ reportedly formed 2-iminothiazolidinones by fusion of β -hydroxyalkylamines, such as ephedrine, with thiourea. Optical activity could be retained in the product from optically active β -hydroxyalkylamines.

A useful synthesis of 5-exomethylene-2-iminothiazolidines (56) has been developed by Thieme and König¹¹⁷ via cyclization of 1-aryl-3-(3-propynyl)-2-thioureas (55).



Base-treatment of the compound proposed to be 1-(2-bromoethyl)-2-thiourea (m.p. $173.6\text{--}174.2^\circ$), formed by the reaction of 2-bromoethylamine hydrobromide with potassium thiocyanate, was reported to yield 2-amino-2-thiazoline;¹¹⁸ however, Klayman¹¹⁹ has shown that the product of the thiocyanate reaction is actually 2-amino-2-thiazoline hydrobromide (m.p. $176\text{--}177^\circ$). 3-(2,3-Dibromopropyl)-2-thioureas were apparently generated *in situ* by addition of bromine to a series of 1,1-disubstituted-3-(2-propenyl)-2-thioureas.¹²⁰ The assumed dibromo intermediates then undergo rapid cyclization to the analogous 5-bromomethyl-2-amino-2-thiazolines. In another ring-closure reaction, Behringer and Zillikens¹²¹ observed that the thiopseudourea derivative 57 cyclized in base to 1,3-thiazines when R was methyl (see Section IV, B, 1); however, when R was hydrogen, then the product was 2-amino-2-thiazoline-4-carboxylic acid (58) in 70% yield.



¹¹⁵ C. K. Bradsher, F. C. Brown, and E. F. Sinclair, *J. Amer. Chem. Soc.* **78**, 6189 (1956).

¹¹⁶ W. Albert, D.D.R. Patent 10,792 (1955); *Chem. Abstr.* **53**, 3243 (1959).

¹¹⁷ P. Thieme and H. König, *Synthesis*, 426 (1973).

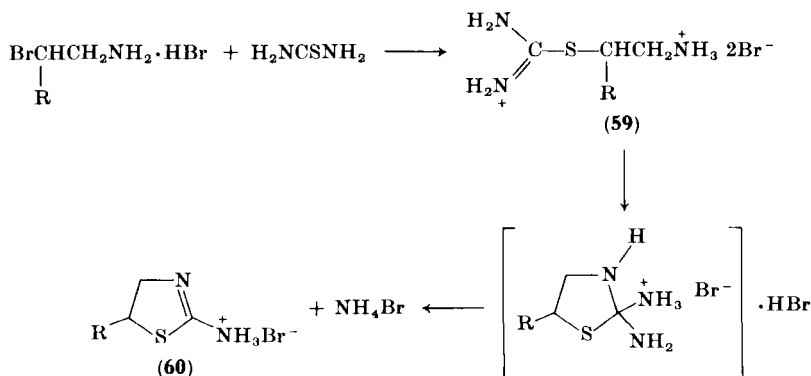
¹¹⁸ E. J. Masters and M. T. Bogert, *J. Amer. Chem. Soc.* **64**, 2709 (1942).

¹¹⁹ D. L. Klayman, unpublished results.

¹²⁰ V. M. Fedoseev and Yu. M. Yevdokimov, *Zh. Obshch. Khim.* **34**, 1551 (1964).

¹²¹ H. Behringer and P. Zillikens, *Justus Liebigs Ann. Chem.* **574**, 140 (1951).

A frequently used method for the construction of the 2-amino-2-thiazoline ring (60) involves the reaction between thiourea and 2-bromoethylamine hydrobromide.¹²²⁻¹²⁴ If the amine nitrogen atom is



substituted, the products are 2-imino-3-substituted thiazolidines.^{125,126} The 2-(2-aminoethyl)thiopseudourea dihydrobromides (59), which are intermediates in the thiourea reaction, have also been used to produce 60 (or 2-imino-3-substituted thiazolidines).^{127,128} In an analogous reaction Chu and Mautner¹²⁹ prepared 2-amino-2-selenazoline from a selenopseudourea salt. A recent Australian patent states that iminothiazolidines are products of the acid treatment of 2-(2-substituted aminoethyl)thiopseudoureas, which were in turn prepared from thiourea and N-substituted aziridines.¹³⁰ Fedoseev *et al.*^{131,132} have

¹²² A. Schöberl and G. Hansen, *Chem. Ber.* **91**, 1239 (1958).

¹²³ V. M. Fedoseev and I. V. Filippovich, *Zh. Obshch. Khim.* **34**, 1561 (1964).

¹²⁴ D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Amer. Chem. Soc.* **79**, 5667 (1957).

¹²⁵ V. M. Fedoseev, V. V. Ivanenkov, and A. B. Silaev, *Zh. Obshch. Khim.* **30**, 3468 (1960).

¹²⁶ W. Fiedler and G. Faust, *J. Prakt. Chem.* **21**, 131 (1963).

¹²⁷ T. Hino, K. Tana-ami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* **14**, 1193 (1966).

¹²⁸ T. Hino, K. Tana-ami, K. Yamada, and S. Akaboshi, *Chem. Pharm. Bull.* **14**, 1201 (1966).

¹²⁹ S.-H. Chu and H. C. Mautner, *J. Org. Chem.* **27**, 2899 (1962).

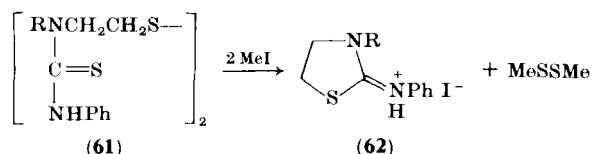
¹³⁰ A. Baklien and J. Kolm, Australian Patent 414,415 (1971); *Chem. Abstr.* **77**, 5449 (1972).

¹³¹ V. M. Fedoseev, S. P. Kovalenko, A. B. Silaev, and A. N. Nesmeyanov, *Zh. Obshch. Khim.* **29**, 1703 (1959).

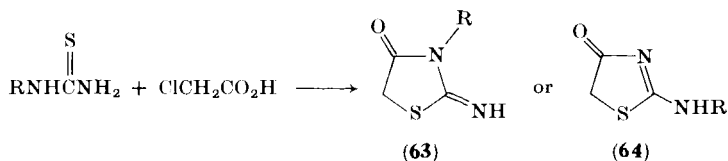
¹³² V. M. Fedoseev, V. N. Bochkarev, and A. B. Silaev, *Zh. Obshch. Khim.* **31**, 3929 (1961).

shown that some bis(thiopseudourea) salts will cyclize to 2-amino-5-(2-thiopseudoureidomethyl)-2-thiazoline dihydrobromides. Kronrád and Kozák¹³³ were able to make the labeled compounds 2-amino-2-thiazoline-2-¹⁴C hydrobromide and 2-amino-2-selenazoline-1-⁷⁵Se hydrobromide from the respective labeled 2-(2-aminoethyl)thio- and selenopseudourea dihydrobromides.

In an interesting reaction reported by Salerni *et al.*,¹³⁴ the disulfide **61** was cleaved by iodomethane at the -CH₂-S- bonds with concomitant cyclization releasing dimethyl disulfide, forming the 2-iminothiazolidine **62**.



One of the more important uses of thioureas has been in the preparation of 2-imino-4-thiazolidinones, first reported by Meyer¹³⁵ and Andreasch,¹³⁶⁻¹³⁸ via reaction with α -halo acids or esters. This reaction has been covered by Brown¹³⁹ in a review on 4-thiazolidinones which appeared in 1961, and, therefore, will not be discussed in detail here. The corresponding reaction between α -halo acids or esters and selenoureas to produce 2-iminoselenazolidin-4-ones is also known and has been reviewed.^{77,78} Åkerblom¹⁴⁰ has attempted to clear up some of the confusion in the literature on whether 3-alkyl-2-iminothiazolidin-4-ones (**63**) or 2-alkylamino-2-thiazolin-4-ones (**64**) are formed from 1-alkylthioureas and chloroacetic acid. She found that the reaction in water



¹³³ L. Kronrád and I. Kozák, *J. Label. Compounds* **9**, 107 (1973).

¹³⁴ O. L. Salerni, J. I. Morrison, W. L. Budde, and C. W. Stanley, *Tetrahedron Lett.*, 5307 (1968).

¹³⁵ P. J. Meyer, *Ber.* **14**, 1659 (1881).

¹³⁶ R. Andreasch, *Monatsh. Chem.* **6**, 821 (1885).

¹³⁷ R. Andreasch, *Monatsh. Chem.* **8**, 407 (1887).

¹³⁸ R. Andreasch, *Ber.* **31**, 137 (1898).

¹³⁹ F. C. Brown, *Chem. Rev.* **61**, 463 (1961).

¹⁴⁰ E. Åkerblom, *Acta Chem. Scand.* **21**, 843 (1967).

with sodium acetate present produced only **64**; whereas, in the absence of base, mixtures of **63** and **64** were obtained. Also **63** could be rearranged to **64** in base and the retro rearrangement could be induced in dilute acid.¹⁴⁰

The reaction of 1-alkyl-3-arylthioureas (or selenoureas) with α -halo esters in the presence of base has been claimed to produce 3-alkyl-2-aryliminothiazolidin-4-ones¹⁴¹⁻¹⁴³ (and the selenium analogs).¹⁴⁴ However, Omar¹⁴⁵ recently reported that a 1-benzyl-3-phenyl-2-thiourea, when treated with ethyl bromoacetate produced a thiazolidinone which has the alkyl side chain on the *exo* nitrogen, i.e., the 3-aryl-2-benzyliminothiazolidin-4-one.

Other preparations of 2-iminothiazolidin-4-ones which are discussed in the review by Brown¹³⁹ utilize the reactions of thiourea with α -hydroxy acids,¹⁴⁶ ethyl diazoacetate,⁷³ glycidic esters,^{74,147} cinnamic acid,¹⁴⁸ unsaturated diacids (fumaric, maleic, and citraconic) or their esters or imides,¹⁴⁹⁻¹⁵² and propiolic esters.^{153,154} There has been considerable controversy in the literature surrounding the propiolic ester synthesis since many workers have proposed that the products are 1,3-thiazines (see Section IV, B, 1). The pertinent papers in this controversy have been summarized by Cain and Warrener.¹⁵⁵ Nagase¹⁵⁶ has recently settled the argument in favor of the 2-iminothiazolidin-4-

¹⁴¹ F. B. Dains, R. D. Coghill, and S. S. Tihen, *Univ. Kansas Sci. Bull* **24**, 25 (1936); *Chem. Abstr.* **32**, 3397 (1938).

¹⁴² F. B. Dains, L. M. Kinsett, C. O. Holmberg, and C. C. Robinson, *Univ. Kansas Sci. Bull.* **24**, 15 (1936); *Chem. Abstr.* **32**, 3396 (1938).

¹⁴³ H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.*, 1022 (1963).

¹⁴⁴ J. Menin, J.-F. Giudicelli, and H. Najer, *C.R. Acad. Sci., Ser. C* **262**, 778 (1966).

¹⁴⁵ A. M. M. E. Omar, *Pharmazie* **28**, 110 (1973).

¹⁴⁶ H. Dannenberg, and A. Rahman, *Chem. Ber.* **89**, 1625 (1956).

¹⁴⁷ J. A. Durden, Jr., H. A. Stansbury, Jr., and W. H. Catlette, *J. Amer. Chem. Soc.* **81**, 1943 (1959).

¹⁴⁸ J. Bougault and P. Chabrier, *C.R. Acad. Sci.* **224**, 656 (1947).

¹⁴⁹ R. Andreasch, *Monatsh. Chem.* **16**, 789 (1895).

¹⁵⁰ R. Andreasch, *Monatsh. Chem.* **18**, 56 (1897).

¹⁵¹ D. H. Marrian, *J. Chem. Soc.*, 1797 (1949).

¹⁵² A. N. Arakelian, H. Dunn, Jr., L. L. Grieshammer, and L. E. Coleman, *J. Org. Chem.* **25**, 465 (1960).

¹⁵³ L. K. Mushkalo and G. Ya. Yangol, *Ukr. Khim. Zh.* **21**, 732 (1955); *Chem. Abstr.* **50**, 16751 (1956).

¹⁵⁴ J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Amer. Chem. Soc.* **86**, 107 (1964).

¹⁵⁵ E. N. Cain and R. N. Warrener, *Aust. J. Chem.* **23**, 51 (1970).

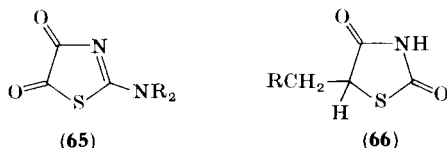
¹⁵⁶ H. Nagase, *Chem. Pharm. Bull.* **21**, 270 (1973).

ones by structure proofs based on preparation of the products via unambiguous routes.

2-Iminothiazolidin-4-ones have also been prepared by the reaction between thiourea and *N*-chloroacetylanilines¹⁵⁷⁻¹⁵⁹ or α -haloacetamides.^{160,161} In addition, these heterocycles are produced by treatment of thiourea with α -trichloromethylbenzyl alcohol¹⁶² and from thio-pseudoureas and thioglycolic acid.¹⁶³

Iwataki⁸³ reported that 1,1-dimethyl-2,4-dithiobiuret formed 3-(*N*, *N*-dimethylthiocarbamoyl)-2-iminothiazolidin-4-one upon reaction with chloroacetyl chloride in acetone in the presence of pyridine; however, the same reaction with sodium acetate used as a base produced 2-(3,3-dimethylthiureido)-2-thiazolin-4-one.⁸³

Goerdeler and Jonas¹⁶⁴ have reported a useful method for the preparation of substituted 2-aminothiazoline-4,5-diones (**65**) by reaction of thioureas with oxalyl chloride. Other diketo products in this series were prepared by cyclization of 2-(α -carbomethoxyalkyl)-2-thiopseudourea hydrobromides in water to form the thiazolidine-2,4-diones **66** probably via hydrolysis of intermediate 2-iminothiazolidin-4-ones.¹⁶⁵



Two reactions have been reported to give thiazolinethiones from thioureas. Gregory and Mathes¹⁶⁶ prepared 4,5-dimethyl-4-thiazoline-2-thione (**67**) via reaction of thiourea with the β -ketothiocyanate **68**. The other reaction was reported by Goerdeler and Lüdke,¹⁶⁷ who

¹⁵⁷ P. J. Meyer, *Ber.* **10**, 1965 (1877).

¹⁵⁸ H. Taniyama and T. Yusa, *J. Pharm. Soc. Jap.* **75**, 5 (1955).

¹⁵⁹ M. Masaki, T. Kitahara, H. Kurita, and M. Ohta, *J. Amer. Chem. Soc.* **90**, 4508 (1968).

¹⁶⁰ V. L. Vasilevskii, V. M. Fedoseev, and A. B. Silaev, *Zh. Obshch. Khim.* **32**, 2269 (1962).

¹⁶¹ K. A. Nuridzhanyan and G. V. Kuznetsova, *Khim. Geterotsikl. Soedin.*, 908 (1970).

¹⁶² W. Reeve and M. Nees, *J. Amer. Chem. Soc.* **89**, 647 (1967).

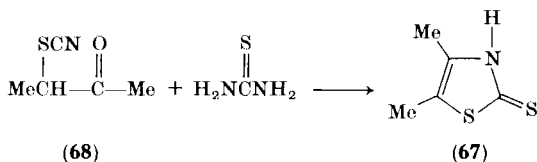
¹⁶³ C. Finzi and C. Angelini, *Ann. Chim. (Rome)* **43**, 832 (1953).

¹⁶⁴ J. Goerdeler and K. Jonas, *Chem. Ber.* **99**, 3572 (1966).

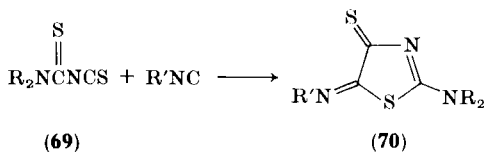
¹⁶⁵ N. N. Suvorov and V. N. Buyanov, *Khim. Geterotsikl. Soedin.*, 377 (1970).

¹⁶⁶ J. T. Gregory and R. A. Mathes, *J. Amer. Chem. Soc.* **74**, 1719 (1952).

¹⁶⁷ J. Goerdeler and H. Lüdke, *Chem. Ber.* **103**, 3393 (1970).



observed that thiocarbamoyl isothiocyanates (69) formed 2-amino-5-imino-2-thiazoline-4-thiones (70) when treated with isocyanides.



2. Two Nitrogen Atoms and One Sulfur Atom

The preparations of 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines from thioureas are well known and have been summarized in three reviews: those of Bambas,¹⁶⁸ Sherman,¹⁶⁹ and Kurzer.¹⁷⁰ Contained in these reviews are discussions of the controversies that surrounded some of the products, notably "Hector's bases," which resulted from oxidation of substituted thioureas.^{171,172} Subjects covered in the above reviews, but too extensive to outline in detail here, are the oxidation of amidinothioureas to 3,5-diamino-1,2,4-thiadiazoles (71),^{173,174} the oxidation of phenylthiourea¹⁷⁵ and of substituted amidinothioureas¹⁷⁶ to 3,5-diimino-1,2,4-thiadiazolidines (72, Hector's bases), the reaction of thiopseudoureas with trichloromethanesulfonyl chloride to form 3-alkylthio-5-chloro-1,2,4-thiadiazoles (73),¹⁷⁷ the reaction of thiopseudoureas with sodium thiocyanate and bromine¹⁷⁸ and the oxidation

¹⁶⁸ L. L. Bambas, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 4, pp. 35-80. Wiley (Interscience), New York, 1952.

¹⁶⁹ W. R. Sherman, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, pp. 541-626. Wiley, New York, 1961.

¹⁷⁰ F. Kurzer, *Advan. Heterocycl. Chem.* **5**, 119 (1965).

¹⁷¹ D. S. Hector, *Ber.* **22**, 1176 (1889).

¹⁷² D. S. Hector, *Ber.* **23**, 357 (1890).

¹⁷³ F. Kurzer, *J. Chem. Soc.*, 1 (1955).

¹⁷⁴ F. Kurzer, *J. Chem. Soc.*, 2288 (1955).

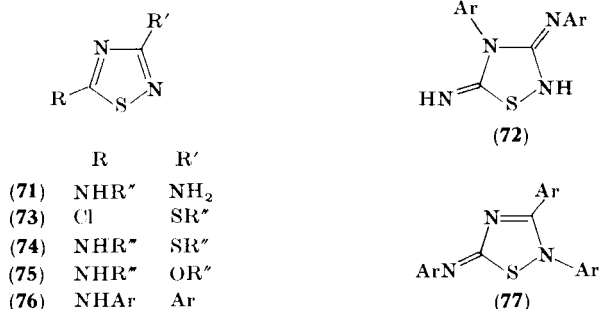
¹⁷⁵ C. P. Joshua, V. K. Verma, and K. S. Suresh, *Tetrahedron Lett.*, 663 (1961).

¹⁷⁶ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 3336 (1963).

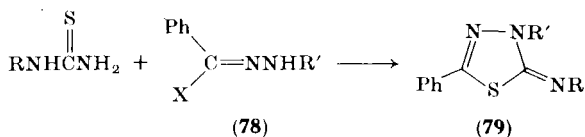
¹⁷⁷ J. Goerdeler and G. Sperling, *Chem. Ber.* **90**, 892 (1957).

¹⁷⁸ J. Goerdeler and P. Linden, *Chem. Ber.* **89**, 2742 (1956).

of dithiopseudobiurets¹⁷⁹ forming 3-alkyl(or aryl)thio-5-amino-1,2,4-thiadiazoles (74), the oxidation of thiobiuret derivatives to 3-alkoxy(or hydroxy)-5-amino-1,2,4-thiadiazoles (75),^{180,181} and the oxidation of *N*-benzimidoyl-*N'*-arylthioureas to 3-aryl-5-arylamino-1,2,4-thiadiazoles (76)¹⁸² or, as was reported recently, to 2,3-diaryl-5-arylimino-1,2,4-thiadiazolines (77).¹⁸³



Freund and Wolf¹⁰ reported that 2,4-diphenyl-1,2,4-thiadiazolidine-3,5-dithione was formed by heating 1,3-diphenyl-2-thiourea with thiophosgene in benzene; whereas, a 1,3-thiazetidine was produced at lower temperatures in ether (see Section II). Chande¹⁸⁴ has reported that 3,5-diamino-1,2,4-thiadiazoles are formed by the reaction of thiopseudoureas with carbon disulfide in the presence of bromine. Use has also been made of thioureas in the synthesis of 1,3,4-thiadiazolines (79) via reaction with the halohydrazones 78.^{185,186} The analogous reaction with selenoureas was recently reported by Bulka and Ehlers¹⁸⁷ to yield 1,3,4-selenadiazolines.



¹⁷⁹ F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 1064 (1959).

¹⁸⁰ F. Kurzer, *Chem. Ind. (London)*, 1482 (1956).

¹⁸¹ F. Kurzer and S. A. Taylor, *J. Chem. Soc.*, 379 (1958).

¹⁸² F. Kurzer and W. Tertiuk, *J. Chem. Soc.*, 2851 (1959).

¹⁸³ G. Barnikow and H. Ebeling, *Z. Chem.* **12**, 130 (1972).

¹⁸⁴ M. S. Chande, *Indian J. Chem.* **8**, 137 (1970).

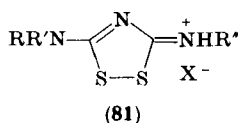
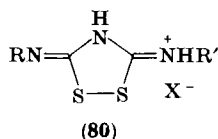
¹⁸⁵ R. Fusco, *Rend. Ist. Lombardo Sci.* **71**, 425 (1938); *Chem. Abstr.* **34**, 3267 (1940).

¹⁸⁶ R. Fusco and C. Musante, *Gazz. Chim. Ital.* **68**, 147 (1938).

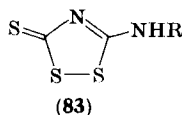
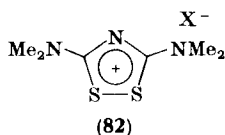
¹⁸⁷ E. Bulka and D. Ehlers, *J. Prakt. Chem.* **315**, 510 (1973).

3. One Nitrogen Atom and Two Sulfur Atoms

In a series of papers, Fromm and co-workers,^{12,64,188,189} beginning in 1893, showed that dithiobiurets could be oxidized with agents such as ferric chloride or halogens to salts of 3,5-diimino-1,2,4-dithiazolines (**80**) or 3-amino-5-imino-5*H*-1,2,4-dithiazoles (**81**). These heterocycles were named "thiurets" by Fromm, and that term has persisted in the later



literature. Verma and co-workers¹⁹⁰⁻¹⁹² prepared **80** and **81** by oxidative debenzoylation of 2-benzyl-2,4-dithiopseudobiurets. The formation and chemistry of thiurets was reviewed by Wuyts,¹⁹³ Bambas,¹⁶⁸ and Kurzer³ in the early 1950's and again by Kurzer¹⁷⁰ in 1965. Bambas¹⁶⁸ presented arguments in favor of a 5-amino-1,2,4-thiadiazolin-3-thione structure for thiurets, but Kurzer¹⁷⁰ disputed Bambas' arguments, and later X-ray studies have confirmed the views of Kurzer in showing that thiuret hydriodide has structure **81** ($R = R' = R'' = H$).^{194,195} The numerous other papers in which thiurets are prepared by previously reported methods will not be discussed here. However, it should be mentioned that tetrasubstituted dithiobiurets were oxidized by Dively¹⁹⁶ and by Oliver *et al.*¹⁹⁷ to dithiazolium salts (**82**).



¹⁸⁸ E. Fromm and E. Junius, *Ber.* **28**, 1096 (1895).

¹⁸⁹ E. Fromm, *Justus Liebigs Ann. Chem.* **361**, 302 (1908).

¹⁹⁰ V. K. Verma, *Indian J. Chem.* **1**, 116 (1963).

¹⁹¹ C. P. Joshua and V. K. Verma, *J. Indian Chem. Soc.* **38**, 988 (1961).

¹⁹² S. N. Dixit and V. K. Verma, *Indian J. Chem.* **1**, 487 (1963).

¹⁹³ H. Wuyts, *Traite Chem. Org.* **21**, 1053 (1953).

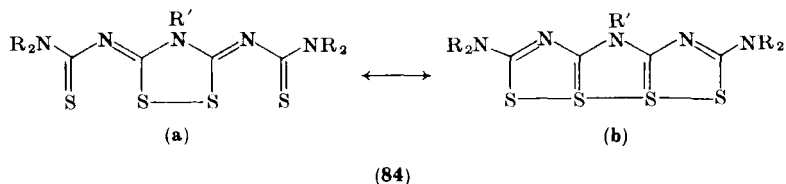
¹⁹⁴ O. Foss and O. Tjomsland, *Acta Chem. Scand.* **12**, 1799 (1958).

¹⁹⁵ P. F. Rodesiler and E. L. Amma, *Acta Crystallogr., Sect. B*, **27**, 1687 (1971).

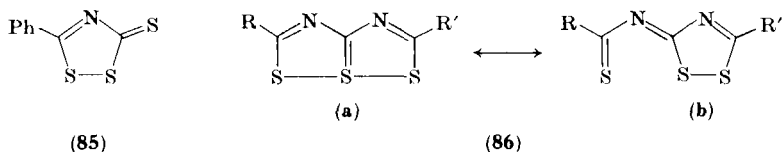
¹⁹⁶ W. R. Diveley, U.S. Patent 3,166,564 (1965); *Chem. Abstr.* **62**, 9145 (1965).

¹⁹⁷ J. E. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Bořkovec, *J. Med. Chem.* **15**, 315 (1972).

The reaction of thioureas with carbon disulfide in the presence of oxygen has been reported to give 3-amino-1,2,4-dithiazole-5-thiones (**83**).¹⁹⁸ The same type of products could also be prepared by treatment of elemental sulfur with thiocarbamoyl isothiocyanates.¹⁹⁹ Reaction of 3-amino-5-imino-1,2,4-dithiazoles with the latter type reagent was reported to yield **84**, the structure of which was postulated as possibly having significant contribution from a "no bond" resonance structure, **84b**.²⁰⁰ However, X-ray studies indicate that structure **84a** is the most important contributor.²⁰¹ A compound of type **84** was also observed as being one of several products, along with 1,2,4-dithiazoles, resulting from the air oxidation of 1,1,5,5-tetramethyl-2,4-dithiobiuret.²⁰²



The reaction of benzoylthiourea with phosphorus pentasulfide was reported to yield 3-phenyl-1,2,4-dithiazole-5-thione (**85**).²⁰³ Derocque *et al.*²⁰⁴ observed that phosphorus pentasulfide converted 1,3-dibenzoyl-2-methyl-2-thiopseudoureas into **86a**. However, in view of the X-ray results on the analogous structure **84**²⁰¹ it may well be that structure **86b** is a more important resonance contributor than **86a**.



¹⁹⁸ J. W. Clapp, T. A. Lies, and G. Lamb, U.S. Patent 3,520,897 (1970); *Chem. Abstr.* **73**, 120636 (1970).

¹⁹⁹ J. E. Oliver, R. T. Brown, and N. L. Redfearn, *J. Heterocycl. Chem.* **9**, 447 (1972).

²⁰⁰ J. Goerdeler and J. Ulmen, *Chem. Ber.* **105**, 1568 (1972).

²⁰¹ J. E. Oliver, J. L. Flippen, and J. Karle, *Chem. Commun.*, 1153 (1972).

²⁰² J. E. Oliver and J. B. Stokes, *Int. J. Sulfur Chem., A* **2**, 105 (1972).

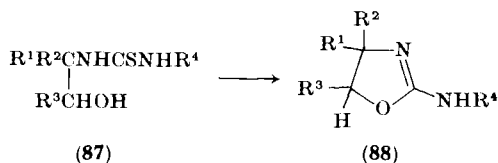
²⁰³ J. Vialle, *Quart. Rep. Sulfur Chem.* **5**, 151 (1970); *Chem. Abstr.* **73**, 109715 (1970).

²⁰⁴ J.-L. Derocque, M. Perrier, and J. Vialle, *Bull. Soc. Chim. Fr.*, 2062 (1968).

C. NITROGEN- AND OXYGEN-CONTAINING RINGS

1. *One Nitrogen Atom and One Oxygen Atom*

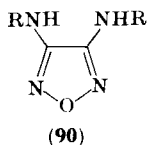
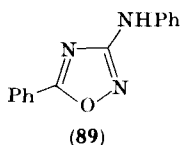
Substituted 2-amino-2-oxazolines (**88**) have been prepared by a number of workers from 1-(2-hydroxyethyl)-2-thioureas (**87**). These



cyclizations have been effected either directly with oxidizing agents^{102,205} or strong acids,¹⁰⁴ or indirectly via conversion of **87** to a 2-methyl-2-thiopseudourea derivative and cyclization of the latter in base,^{22,206,207} or simply by heating in polar solvents if R⁴ is activating.²⁰⁸ Weygand *et al.*^{208a} reported that treatment of ethyl lactate with thiourea in the presence of base yielded 5-methyloxazolidin-4-one-2-thione.

2. *Two Nitrogen Atoms and One Oxygen Atom*

Two of the three possible isomeric ring systems of this type are reportedly formed from thioureas. Yang and Johnson²⁰⁹ prepared the 1,2,4-oxadiazole **89** by treatment of 1-benzoyl-2-methyl-3-phenyl-2-thiopseudourea with hydroxylamine. The unstable *N*-hydroxythioureas resulting from reaction of isothiocyanates with hydroxylamine were claimed by Guha and Chakladar²¹⁰ to decompose to the unlikely 1,2,5-oxadiazoles **90**.



²⁰⁵ Y. Iwakura, T. Kaya, and K. Kurita, *Bull. Chem. Soc. Jap.* **43**, 2531 (1970).

²⁰⁶ B. Adcock and A. Lawson, *J. Chem. Soc. C*, 65 (1966).

²⁰⁷ B. Adcock, A. Lawson, and D. H. Miles, *J. Chem. Soc.*, 5120 (1961).

²⁰⁸ D. L. Klayman, R. J. Shine, and A. E. Murray, Jr., *J. Pharm. Sci.* **59**, 1515 (1970).

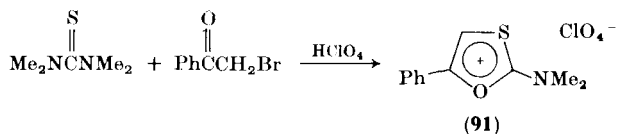
^{208a} F. Weygand, H. J. Bestmann, and F. Steden, *Chem. Ber.* **91**, 2537 (1958).

²⁰⁹ S. T. Yang and T. B. Johnson, *J. Amer. Chem. Soc.* **54**, 2066 (1932).

²¹⁰ P. C. Guha and M. N. Chakladar, *Proc. Indian Sci. Congr.* **15th**, 157 (1928); *Chem. Abstr.* **25**, 2999 (1931).

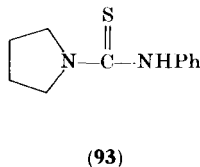
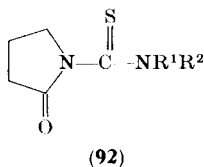
D. OXYGEN- AND SULFUR-CONTAINING RINGS

The single report of an oxygen- and sulfur-containing five-membered ring formed from a thiourea is that of Hartmann,²¹¹ who prepared the 1,3-oxathiolium salt **91** from α -bromoacetophenone and tetramethylthiourea.



E. MISCELLANEOUS FIVE-MEMBERED RINGS

A number of interesting five-membered ring heterocycles of other types have been reported in the literature as having been derived from thioureas. The pyrrolidin-2-ones **92** were formed by cyclization of 1-(4-bromobutanoyl)-2-thioureas.²¹² In a related reaction, Cherbuliez¹⁰⁶ produced the pyrrolidine **93** by treatment of the sulfate ester of 1-(4-hydroxybutyl)-3-phenyl-2-thiourea with acid or base.



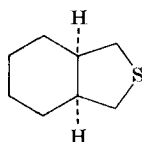
Thiolanes have been prepared by cyclization of 2-(3-hydroxyalkyl)-2-thiopseudoureas with base,⁶ a reaction which has also been used to prepare thiiranes and thietanes (see previous sections.)⁶ Lüttringhaus and Brechlin²¹³ reported the formation of *cis*-2-thiahydrindane (**94**) by treatment of *cis*-1,2-bis(bromomethyl)cyclohexane with 2 moles of thiourea. The *trans* dibromide, however, failed to give the analogous product. Winterfeldt²¹⁴ discovered that one of the by-products of the reaction of dimethylpropiolate with 1,1,3,3-tetramethyl-2-thiourea was the thiophene **95**.

²¹¹ H. Hartmann, D.D.R. Patent 77,732 (1970); *Chem. Abstr.* **75**, 151744 (1971).

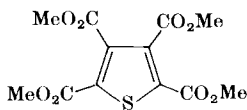
²¹² D. N. Reinhoudt, *Rec. Trav. Chim.*, **92**, 20 (1973).

²¹³ A. Lüttringhaus and A. Brechlin, *Chem. Ber.* **92**, 2271 (1959).

²¹⁴ E. Winterfeldt, *Chem. Ber.* **100**, 3679 (1967).

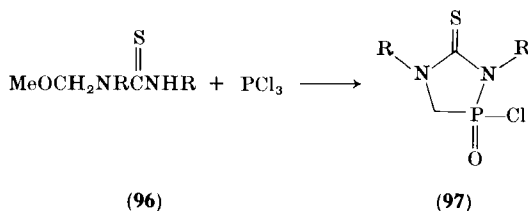


(94)



(95)

A single example of a phosphorus-containing heterocycle made from a thiourea is the 1,3,4-diazaphospholane (97) prepared in 80% yield via treatment of 96 with phosphorus trichloride.²¹⁵



(96)

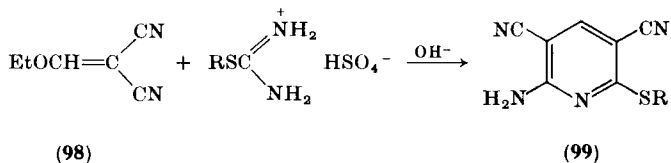
(97)

IV. Six-Membered Rings

A. NITROGEN-CONTAINING RINGS

1. One Nitrogen Atom

The sole report in the literature of a pyridine nucleus prepared from thioureas is that of Cottis and Tieckelmann,²¹⁶ who obtained 2-amino-3,5-dicyano-6-alkylthiopyridines (99) by treating 2-alkyl-2-thiopseudo-urea hydrogen sulfates with 1,1-dicyano-2-ethoxyethene (98). Careful attention to the concentration of 98 and base led to good yields of 99; otherwise, the products of the reaction were pyrimidines.²¹⁶



(98)

(99)

²¹⁵ H. Petersen, U.S. Patent 3,673,248 (1972); *Chem. Abstr.* **77**, 101892 (1972).

²¹⁶ S. G. Cottis and H. Tieckelmann, *J. Org. Chem.* **26**, 79 (1961).

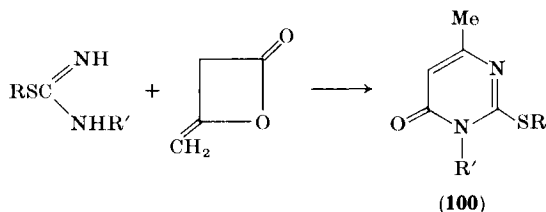
2. Two Nitrogen Atoms

The preparation of pyrimidines and hydropyrimidines from thioureas is well established.^{139,217,218} Since the latest review (1962) covering this reaction,²¹⁸ several reports of the preparation of heterocyclic compounds by previously reported procedures have appeared in the literature. These involve reactions of thioureas with α,β -unsaturated ketones,²¹⁹⁻²²⁴ β -ketoesters,²²⁵⁻²²⁸ aliphatic ketones,²²⁹⁻²³¹ β -dicarbonyl compounds,²³² and ethyl ethoxymethylenecyanoacetate.²³³ Selenoureas have also been reported to react with β -ketoesters to give the analogous 2-selenopyrimidines.^{234,235} Two reports have appeared of the cyclization of 1- β -carboxyethyl-2-thioureas to hexahydropyrimidines in low yields in the presence of acetic anhydride;^{236,237} however, tetrahydrothiazines are the predominant products in these reactions.

An innovation in the synthesis of pyrimidines was reported by Lacey

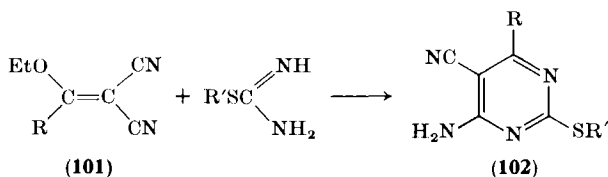
- ²¹⁷ G. W. Kenner and Sir Alexander Todd, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, pp. 234-323. Wiley, New York, 1957.
- ²¹⁸ D. J. Brown, in "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 16, pp. 82-111. Wiley (Interscience), New York, 1962.
- ²¹⁹ R. Zimmermann, *Angew. Chem.* **75**, 1124 (1963).
- ²²⁰ E. J. Nikawitz, U.S. Patent 3,152,122 (1964); *Chem. Abstr.* **62**, 1670 (1965).
- ²²¹ A. E. Sammour and M. El-Kasaby, *U.A.R. J. Chem.* **12**, 17 (1969).
- ²²² A. E. Sammour, M. I. B. Selim, M. M. Nonr El-Deen, and M. Abd-El-Halim, *U.A.R. J. Chem.* **13**, 7 (1970); *Chem. Abstr.* **75**, 5840 (1971).
- ²²³ R. M. Khachatryan and S. A. Vartanyan, *Arm. Khim. Zh.* **25**, 338 (1972); *Chem. Abstr.* **77**, 125923 (1972).
- ²²⁴ A. E. Sammour, M. I. B. Selim, M. El-Kasaby, and F. Saied, *J. Prakt. Chem.* **314**, 941 (1972).
- ²²⁵ H. M. Foster, and H. R. Snyder, in "Organic Syntheses" (N. Rabjohn, ed.), Coll. Vol. 4, pp. 638-640. Wiley, New York, 1963.
- ²²⁶ A. O. Fitton and R. K. Smalley, "Practical Heterocyclic Chemistry," p. 104. Academic Press, New York, 1968.
- ²²⁷ R. Neidlein and G. Menche, *Arch. Pharm. (Weinheim)* **305**, 596 (1972).
- ²²⁸ G. Heinisch, *Monatsh. Chem.* **104**, 953 (1973).
- ²²⁹ H. Hartmann and R. Mayer, *J. Prakt. Chem.* **30**, 87 (1965).
- ²³⁰ G. Jaenecke, *Z. Chem.* **6**, 109 (1966).
- ²³¹ G. Zigeuner, G. Gübitz, and V. Eisenreich, *Monatsh. Chem.* **101**, 1686 (1970).
- ²³² T. Nagasawa, K. Kuroiwa, K. Narita, and Y. Isowa, *Bull. Chem. Soc. Jap.* **46**, 1269 (1973).
- ²³³ T. L. V. Ulbright, T. Okuda, and C. C. Price, in "Organic Syntheses" (N. Rabjohn, ed.), Coll. Vol. 4, p. 566. Wiley, New York, 1963.
- ²³⁴ H. G. Mautner, *J. Amer. Chem. Soc.* **78**, 5292 (1956).
- ²³⁵ H. G. Mautner and E. M. Clayton, *J. Amer. Chem. Soc.* **81**, 6270 (1959).
- ²³⁶ M. Deržaj-Bizjak, S. Oblak and M. Tišler, *J. Org. Chem.* **27**, 1343 (1962).
- ²³⁷ A. Prosen, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **29**, 1624 (1964).

in 1953²³⁸ and amplified in a subsequent paper.²³⁹ The reaction involves treatment of 2-alkyl-2-thiopseudoureas with diketene, usually in aqueous base, to give 3,4-dihydro-2-alkylthio-6-methyl-4-pyrimidinones (**100**). Recent work by Veronese and D'Angeli²⁴⁰ has indicated



that if high temperatures are used, the products are dihydro-1,3-oxazinones resulting from rearrangement of **100**. Richter and Ulrich²⁴¹ have confirmed that compounds of type **100** may be prepared from thioureas by this procedure.

A useful preparation of pyrimidines from thioureas, which has recently been summarized in a monograph by Taylor and McKillop,²⁴² involves the reaction of ethoxymethylenemalonitriles (**101**) with 2-alkyl-2-thiopseudoureas to form 2-alkylthio-6-amino-5-cyanopyrimidines (**102**). In addition, the above-mentioned work²⁴³ critically



evaluates the reaction of enamionitriles (**103**) with thiourea to give 1,2-dihydro-4-amino-2-pyrimidinethiones (**104**).

In a variation of the β -carbonylester synthesis of pyrimidines from thioureas (see above), Fissekis and Sweet²⁴⁴ recently reported the reaction of the methoxyacetalester **105** with thiourea in methanolic sodium methoxide to give four new hydropyrimidines, **106–109**, in low yield. When sodium *t*-butoxide was used, only **107** was produced.

²³⁸ R. N. Lacey, British Patent 699,812 (1953); *Chem. Abstr.* **49**, 2527c (1955).

²³⁹ R. N. Lacey, *J. Chem. Soc.*, 839 (1954).

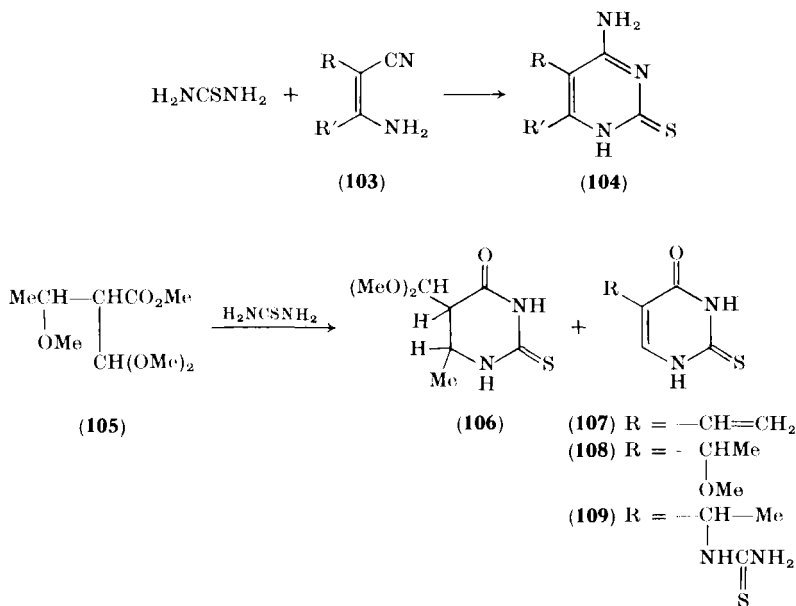
²⁴⁰ A. C. Veronese and F. D'Angeli, *Ann. Chim. (Rome)* **60**, 374 (1970).

²⁴¹ R. Richter and H. Ulrich, *Chem. Ber.* **106**, 1501 (1973).

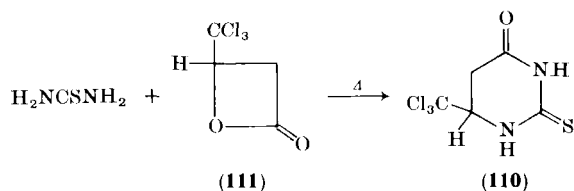
²⁴² E. C. Taylor and A. McKillop in "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," pp. 113–118. Wiley (Interscience), New York, 1970.

²⁴³ E. C. Taylor and A. McKillop, in "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," p. 295. Wiley, (Interscience), New York, 1970.

²⁴⁴ J. D. Fissekis and F. Sweet, *J. Org. Chem.* **38**, 1963 (1973).



Luknitskii *et al.*²⁴⁵ reported preparation of the hexahydropyrimidin-4-one-2-thione **110** by fusion of thiourea with 4-trichloromethyl-2-oxetanone (**111**) at 110–130°. Performing the reaction in ethanolic triethylamine gave an oxazine product instead. With selenopseudoureas, **111** gives 1,3-selenazines.²⁴⁶

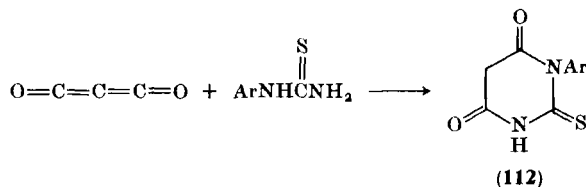


A promising new method for the preparation of thiobarbituric acids (**112**) involving the reaction of carbon suboxide with various arylthioureas was reported by Baranova *et al.*²⁴⁷

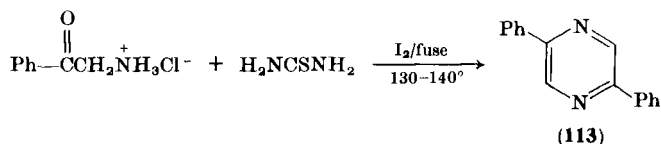
²⁴⁵ F. I. Luknitskii, D. O. Taube, and B. A. Vovsi, *Zh. Org. Khim.* **5**, 1844 (1969).

²⁴⁶ F. I. Luknitskii, D. O. Taube, and B. A. Vovsi, *Dokl. Akad. Nauk SSSR* **184**, 355 (1969).

²⁴⁷ N. A. Baranova, V. G. Beilin, and L. B. Dashkevich, *Zh. Org. Khim.* **6**, 1734 (1970).



Only one report of a pyrazine-type compound apparently utilizing a thiourea has appeared. Tashika and Nitta²⁴⁸ found that the iodine/thiourea oxidation of α -aminoacetophenone hydrochloride gave 2,5-diphenylpyrazine (113). The authors do not discuss the mechanism nor the function of the molar quantity of thiourea in the reaction.



3. Three Nitrogen Atoms

The chemistry leading to the formation of *s*-triazines from thioureas has been of considerable interest historically, and is well summarized in a monograph by Smolin and Rapoport²⁴⁹; thus the newer or less common aspects of these reactions will be dealt with here.

One of the most convenient methods of preparing *s*-triazines from thioureas is by the action of acyl isothiocyanates on 2-thiopseudoureas, first studied by Johnson *et al.*²⁵⁰ and later by Douglass and Dains.²⁵¹ A recent report of this reaction was made by Goerdeler and Neuffer,²⁵² who prepared a series of *s*-triazinethiones (115) by treating 2-thiopseudoureas with benzoyl isothiocyanate (114, R = Ph). These authors²⁵³ also studied the reaction of carbethoxy isothiocyanate (114, R = EtO) with 2-thiopseudoureas to prepare several 2-alkylthio-*s*-triazin-6-one-4-thiones (116). A unique *s*-triazine-producing reaction involving isothiocyanates was studied by Ghosh and Guha,²⁵⁴ who

²⁴⁸ Y. Tashika and Y. Nitta, *J. Pharm. Soc. Jap.* **72**, 1157 (1952).

²⁴⁹ E. M. Smolin and L. Rapoport, "The Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 13. Wiley (Interscience), New York, 1959.

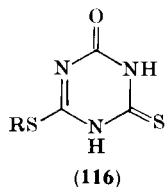
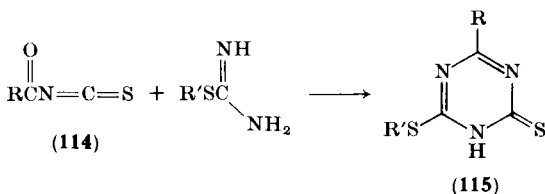
²⁵⁰ T. B. Johnson, H. S. Bristol, M. S. Elmer, and W. B. Cramer, *Amer. Chem. J.* **30**, 167 (1903).

²⁵¹ I. B. Douglas and F. B. Dains, *J. Amer. Chem. Soc.* **56**, 719 (1934).

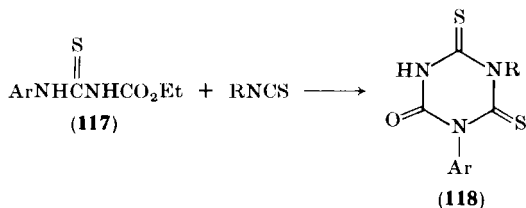
²⁵² J. Goerdeler and J. Neuffer, *Chem. Ber.* **104**, 1580 (1971).

²⁵³ J. Goerdeler and J. Neuffer, *Chem. Ber.* **104**, 1606 (1971).

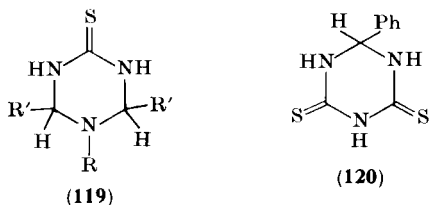
²⁵⁴ T. N. Ghosh and P. C. Guha, *J. Indian Chem. Soc.* **7**, 263 (1930).



found that 1-carbethoxy-3-aryl-2-thiureas (117) on treatment with isothiocyanates yield the dithiocyanuric acid derivatives 118.



A useful preparation of *s*-triazines from thiureas which has received scant attention in the literature is to be found in the work of Burke,²⁵⁵ who discovered that treatment of thiurea with aldehydes in the presence of amines leads to hexahydro-*s*-triazinethiones (119) in high yields. The starting thiurea may be 1,3-disubstituted, and the amines



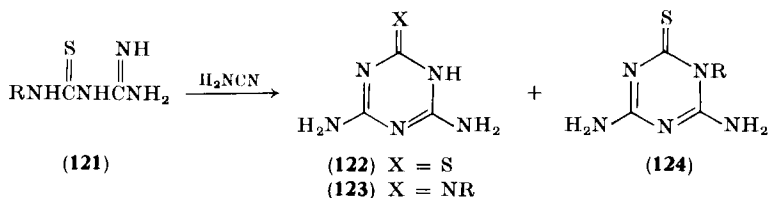
and aldehydes may be widely varied in structure without deterring the cyclization. Steindorff and Paquin²⁵⁶ had previously proposed a

²⁵⁵ W. J. Burke, *J. Amer. Chem. Soc.* **69**, 2136 (1947).

²⁵⁶ A. Steindorff and M. Paquin, U.S. Patent 2,016,521 (1935); *Chem. Abstr.* **29**, 8182 (1935).

similar process leading to **119** ($R' = \text{Me}$, $R = \text{H}$) by treating thiourea with the acetaldehyde-ammonia adduct. This reaction had been studied by Nencki²⁵⁷ in 1874, who mistakenly formulated the product as "Diäthylidenesulfoharnstoff." Furthermore, Ahmed and Subba Rao²⁵⁸ have reported that the reaction also proceeds with ammonium acetate in place of the amine and with various aromatic aldehydes ($R'\text{CHO}$) to give **119** ($R = \text{H}$). Similar results were reported by Krässig and Egar²⁵⁹ when thiourea was heated with benzaldehyde without an amine present to give **119** ($R' = \text{Ph}$, $R = \text{H}$) and an alcohol-insoluble polymer. When the reaction was carried out under a nitrogen atmosphere the product was **120**. Several groups have studied the formation of products analogous to **120** by the interaction of aldehydes with various mono-²⁶⁰ and dithiobiurets^{13,261} in the presence of acid catalysts; thus, dithiobiuret itself would seem to be a likely intermediate in the formation of **120**. Davidson⁵¹ has replaced the aldehydes in the dithiobiuret reactions with acetone and prepared the 6,6-dimethyl analogs of **120**, as did Chase and Walker²⁶² in the thiopseudourea series. Foye and Hefferren²⁶³ also studied the reaction of dithiobiuret with various aromatic aldehydes and with 1-propanal; however, they incorrectly assigned a linear Schiff base structure to the products.

s-Triazines may also be prepared by treatment of amidinothioureas **121** with cyanamide as reported by Kurzer and Pitchfork,²⁶⁴ who found that the ratios of the three products **122**, **123**, and **124** could be controlled by varying temperature and solvent. The authors speculated



²⁵⁷ M. Nencki, *Ber.* **7**, 158 (1874).

²⁵⁸ K. Ahmed and N. V. Subba Rao, *Proc. Indian Acad. Sci., Sect. A* **55**, 284 (1962); *Chem. Abstr.* **58**, 4569 (1963).

²⁵⁹ H. Krässig and G. Egar, *Makromol. Chem.* **18/19**, 195 (1956); *Chem. Abstr.* **51**, 758 (1957).

²⁶⁰ J. S. Davidson, personal communication.

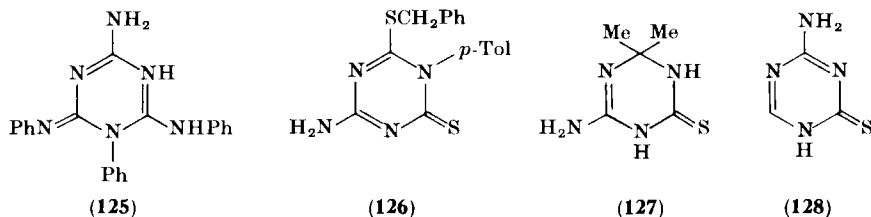
²⁶¹ E. E. Smissman, G. J. Hite, and W. O. Foye, *J. Org. Chem.* **22**, 824 (1957).

²⁶² B. H. Chase and J. Walker, *J. Chem. Soc.*, 4443 (1955).

²⁶³ W. O. Foye and J. J. Hefferren, *J. Amer. Pharm. Ass.* **42**, 31 (1953); *Chem. Abstr.* **47**, 3524 (1953).

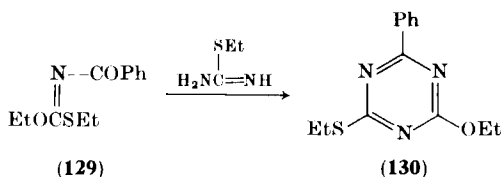
²⁶⁴ F. Kurzer and E. D. Pitchfork, *J. Chem. Soc.*, 6296 (1965).

that formation of the products was via an unisolated biguanidothiurea intermediate and have also reported the reaction of **121** ($R = Ph$) with diphenylcarbodiimide to give the triphenyl derivative **125**.²⁶⁵ A novel reaction of an amidinothiurea with carbon disulfide has been recently reported²⁶⁶ to yield **126** in addition to a thiadiazine product. In the

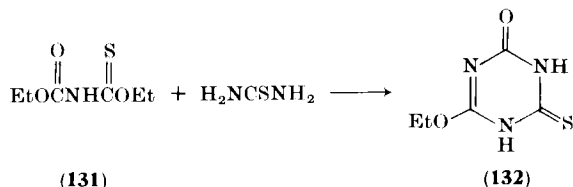


earlier literature, Chase and Walker²⁶² studied the interaction of amidinothiurea with acetone in the presence of piperidine to give a similar product **127**. Another useful triazine preparation from amidinothiurea (**121**) is detailed in the work of de Lannoy and Nasielski-Hinkens,²⁶⁷ who reported the formation of **128** in 83% yield by treating **121** ($R = H$) with ethyl formate in the presence of strong base.

Another type of reaction leading to *s*-triazines from thioureas is that of Johnson and Menge,²⁶⁸ who reported that the imidothiocarbonate **129**, when treated with 2-ethyl-2-thiopseudoourea, gave the triazine



product **130**. Another starting material was employed by Guha *et al.*,²⁶⁹ who prepared **132** by treating **131** with thiourea.



²⁶⁵ F. Kurzer and E. D. Pitchfork, *J. Chem. Soc. C*, 1878 (1967).

²⁶⁶ J. D. Dhake, *J. Indian Chem. Soc.* **49**, 1151 (1972).

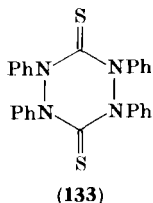
²⁶⁷ J. de Lannoy and R. Nasielski-Hinkens, *Bull. Soc. Chim. Belges* **81**, 587 (1972).

²⁶⁸ T. B. Johnson and G. A. Menge, *Amer. Chem. J.* **32**, 358 (1904).

²⁶⁹ P. C. Guha, S. Rao, and A. Saletone, *J. Indian Chem. Soc.* **6**, 565 (1929).

4. Four Nitrogen Atoms

The only report in the literature of the preparation of a tetrazine from a thiourea is that of Naik,²⁷⁰ who claimed to have isolated hexahydro-1,2,4,5-tetraphenyl-1,2,4,5-tetrazine-3,6-dithione (**133**) on treatment of 1,3-diphenyl-2-thiourea with sulfur monochloride in refluxing benzene. Since the only evidence presented for structure **133**

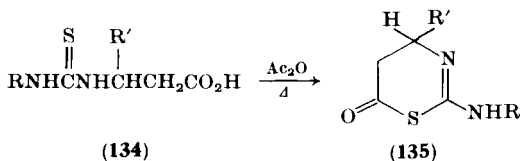


was an elemental analysis, alternative structures cannot be ruled out. Further work on this reaction is warranted.

B. NITROGEN- AND SULFUR-CONTAINING RINGS

1. One Nitrogen Atom and One Sulfur Atom

The preparation of 1,3-thiazines utilizing thioureas has been reviewed²⁷¹ and also is briefly summarized in a paper by Cain and Warrener.¹⁵⁵ The 1,3-thiazine ring system may be prepared by intramolecular cyclization of variously substituted propylthioureas. Several groups have studied the behavior of 1-(2-carboxyethyl)-2-thiourea derivatives (**134**) on heating in the presence of acetic anhydride to give **135**. Ghosh²⁷² claimed to isolate solely products of type **135** in good yield; whereas, Deržaj-Bizjak²³⁶ and Prosen²³⁷ and their co-workers



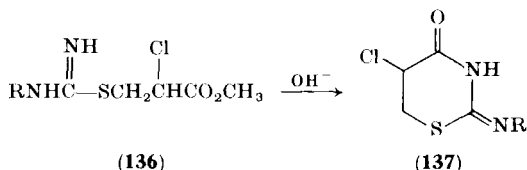
obtained mixtures of **135** and pyrimidines, the former being favored by prolonged heating.²³⁶ Behringer and Zillikens¹²¹ reported that treat-

²⁷⁰ K. G. Naik, *J. Chem. Soc.* **119**, 1166 (1921).

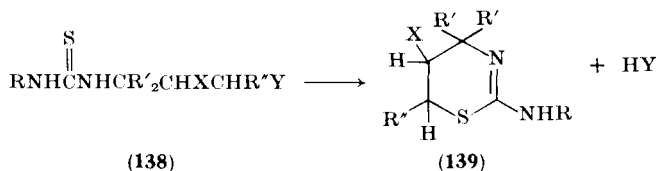
²⁷¹ R. C. Elderfield and E. E. Harris, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, pp. 601-623. Wiley, New York, 1957.

²⁷² T. N. Ghosh, *J. Indian Chem. Soc.* **11**, 23 (1934).

ment of the thiopseudourea ester **136** with aqueous alkali gave the tetrahydro-1,3-thiazines **137** ($R = H, Et$).



Several workers have studied other cyclization reactions involving various leaving groups. Thus, compounds **138** have been shown to cyclize to 1,3-thiazines (**139**) under acidic or alkaline conditions. The earliest recorded reaction of this type is that of Kahan,²⁷³ who in 1897



reported the cyclization of **138** ($R = \text{Ph}$ or Et , $R' = R'' = \text{Me}$, $X = \text{H}$, $Y = \text{OH}$) to the analogous **139** in concentrated hydrochloric acid. Later workers²⁷⁴ utilized the same reaction type to prepare other compounds in the series, and in 1967 Cherbuliez *et al.*²⁷⁵ studied these reactions and found by NMR model studies that on cyclization of various **138** ($R' = R'' = X = \text{H}$, $Y = \text{OH}$), the exocyclic position of the C-N double bond is favored in the product if R is aromatic and the endocyclic position if R is aliphatic. Cherbuliez and his associates also reported cyclization of **138** where $Y = \text{OPO}_3\text{H}_2$ ¹⁰⁵ and OSO_3H .¹⁰⁶ Other workers^{132,276,277} have studied a similar process in the analogous thiopseudourea series ($Y = \text{NH}_2$) leading to 1,3-thiazines, including an analysis of the kinetics of the cyclization.²⁷⁸

The 1,3-thiazine ring system may be prepared by treating various

²⁷³ M. Kahan, *Ber.* **30**, 1318 (1897).

²⁷⁴ F. B. Dains, R. Q. Brewster, J. S. Blair, and W. C. Thompson, *J. Amer. Chem. Soc.* **44**, 2637 (1922).

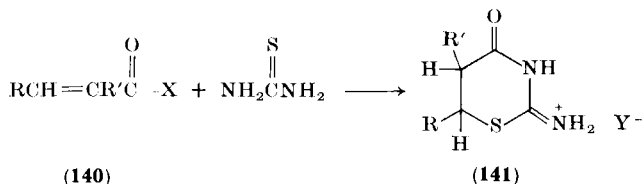
²⁷⁵ E. Cherbuliez, Br. Baehler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabino-witz, *Helv. Chim. Acta* **50**, 331 (1967).

²⁷⁶ V. M. Fedoseev, G. N. Shalacva, and V. I. Pershin, *Zh. Org. Khim.* **4**, 1791 (1968).

²⁷⁷ V. M. Fedoseev and I. V. Filippovich, *Zh. Obshch. Khim.* **34**, 1556 (1964).

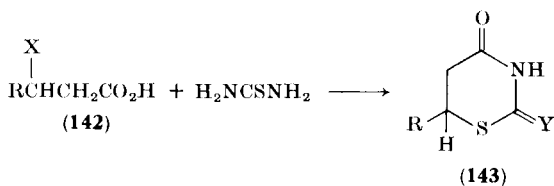
²⁷⁸ V. M. Fedoseev and V. S. Churilin, *Zh. Org. Khim.* **8**, 2434 (1972).

α,β -unsaturated carboxylic acid derivatives (**140**) with thioureas. Using this reaction Nomura *et al.*²⁷⁹ prepared the tetrahydroiminothiazinone **141** ($R = R' = H$, $Y = Cl$) by treating thiourea with acryloyl chloride



(**140**, $R = R' = H$, $X = Cl$). Taborsky²⁸⁰ also used this method to prepare the substituted **141** ($R = Ph$, $R' = Et$, $Y = \text{HSO}_4$) from α -ethyleinnamic acid (**140**, $R = Ph$, $R' = Et$, $X = OH$); similar work was performed by Takemoto *et al.*²⁸¹ These reaction types are discussed briefly in a review of 4-thiazolidinones by Brown.¹³⁹ Overberger and Friedman²⁸² were able to show that 1,3-diphenyl-2-thiourea also undergoes this reaction to give the 3-phenyl-2-phenylimino analog of **141**. Results similar to the above were reported by Zimmermann,²⁸³ who prepared **141** [$R = \text{CO}_2R''$ ($R'' =$ various aliphatic groups), $R' = H$, $Y = Cl$ or Br]. Akashi *et al.*²⁸⁴ studied a similar process in their report of the interaction of **140** ($R = H$, $R' = \text{CH}_2\text{CO}_2H$, $X = OH$) with thiourea to give an analog of **141** ($R = H$, $R' = \text{CH}_2\text{CO}_2H$) which contains a 2-carbonyl rather than 2-imino group. Also, triazines are formed on BF_3 treatment of α,β -unsaturated carbonyl compounds and thioureas.²⁸⁵

Many workers have employed β -halocarboxylic acids (**142**) to prepare tetrahydro-1,3-thiazines (**143**) from thioureas. The halogen atom (X)



²⁷⁹ M. Nomura, Y. Nagano and K. Teramura, *Yuki Gosei Kagaku Kyokai Shi* **30**, 971 (1972); *Chem. Abstr.* **78**, 84342 (1973).

²⁸⁰ R. G. Taborsky, *J. Org. Chem.* **23**, 1779 (1958).

²⁸¹ K. Takemoto, H. Tahara, Y. Inaki, and N. Ueda, *Chem. Lett.*, 767 (1972); *Chem. Abstr.* **77**, 139953w (1972).

²⁸² C. G. Overberger, and H. A. Friedman, *J. Org. Chem.* **29**, 1720 (1964).

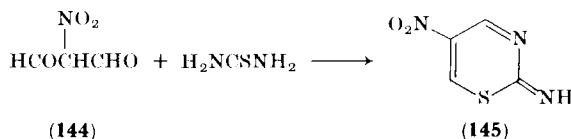
²⁸³ R. Zimmermann, *Angew. Chem. Int. Ed. Engl.* **1**, 663 (1962).

²⁸⁴ H. Akashi, R. Masuda, C. Katsuda, and T. Kobayashi, *Mem. Fac. Eng., Kobe Univ.*, 151 (1970); *Chem. Abstr.* **73**, 3433m (1970).

²⁸⁵ S. Hoff and A. P. Blok, *Rec. Trav. Chim.* **92**, 631 (1973).

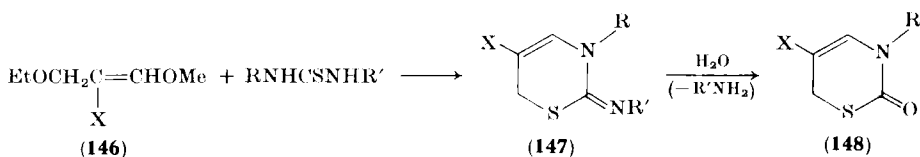
may be chlorine,^{286,287} bromine,^{148,288} or iodine,²⁸⁹ and the second β -substituent (R) may be hydrogen,^{286,287,289} aryl,²⁸⁸ or aryl¹⁴⁸ (Y of **143** may be NH or O).

Two groups have reported preparation of 1,3-thiazines beginning with β -dicarbonyl compounds. The reaction of thiourea with 2-nitropropanedial **144** was reported by Hale and Brill²⁹⁰ to give **145**. Similar



work involving both β -dialdehydes and β -diketones was reported later by Hartmann.²⁹¹ Heterocycles containing only one double bond analogous to **145** are obtained when thiureas react with α,β -unsaturated ketones or β -hydroxy ketones²⁹² or with acetone²⁶² (probably via intermediate mesityl oxide).

Takamizawa *et al.*^{293,294} have reported the investigation of the reaction of the unsaturated diethers **146** with variously substituted thiureas to give dihydrothiazinones **148**. The substituent may be carbethoxy (X = CO₂Et)²⁹⁴ or cyano (X = CN),²⁹³ and in the former case it was possible to isolate the 2-imino intermediate **147** (X = CO₂Et)



Other useful reagents for the preparation of tetrahydro-1,3-thiazines with a 5-hydroxy substituent (**149**) are 3-chloro-²⁹⁵ or 3-phthalimido-²⁹⁶

²⁸⁶ Ye. V. Vladzimirskaya and N. M. Turkevich, *Mater. Pervogo Vseross. S'ezda Farm. (Moscow: Med) Sb.*, 298 (1962); *Chem. Abstr.* **63**, 2967g (1965).

²⁸⁷ N. M. Turkevich, Ye. V. Vladzimirskaya, and L. M. Vengrinovich, *Khim. Geterotsikl. Soedin.*, 504 (1969).

²⁸⁸ K. W. Wheeler and V. W. Gash, U. S. Patent 2,585,064 (1952); *Chem. Abstr.* **46**, 7593 (1952).

²⁸⁹ N. A. Langlet, *Ber.* **24**, 3848 (1891).

²⁹⁰ W. J. Hale and H. C. Brill, *J. Amer. Chem. Soc.* **34**, 295 (1912).

²⁹¹ H. Hartmann, *Tetrahedron Lett.*, 3977 (1972).

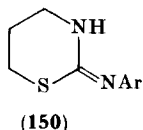
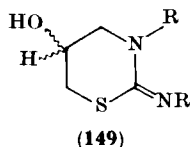
²⁹² R. Zimmermann, *Angew. Chem.* **75**, 1025 (1963).

²⁹³ A. Takamizawa, K. Hirai, Y. Sato, and K. Tori, *J. Org. Chem.* **29**, 1740 (1964).

²⁹⁴ A. Takamizawa and K. Hirai, *J. Org. Chem.* **30**, 2290 (1965).

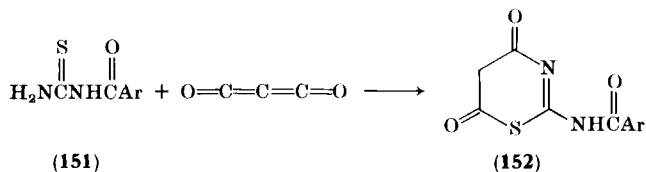
²⁹⁵ F. G. Moore and F. B. Dains, *Univ. Kansas Sci. Bull.* **18**, 633 (1928); *Chem. Abstr.* **24**, 2133 (1930).

epoxides, which on reaction with thioureas produce the products **149** ($R = H$ ²⁹⁶ or aryl²⁹⁵).

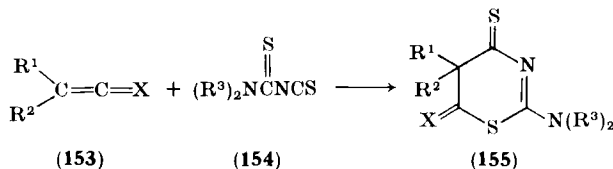


An interesting rearrangement of thioureas leading to tetrahydro-1,3-thiazines has been reported by Tišler,^{297,298} who found that 1-trimethylene-3-aryl-2-thioureas undergo facile conversion to **150** in concentrated HCl. The same products (**150**) could also be prepared by treating the appropriately substituted thiourea with 1,3-dibromopropane.²⁹⁸

A preparation of the thiazine ring system which should be investigated for generality is that of Baranova *et al.*,²⁴⁷ who interacted the 1-aryl-2-thioureas **151** with carbon suboxide to give **152**. Compounds of structure similar to **152** were also obtained starting with 1,1-disubstituted thioureas.²⁴⁷ Treatment of other cumulenes **153**, ketenes ($X = O$)



and ketenimines ($X = NR'$), with thiocarbamoyl isothiocyanates (**154**) was reported by Goerdeler and Lüdke¹⁶⁷ to lead to **155**. They also found that bicyclic 1,3-thiazines were formed on treatment of **154** with cyclic enamines.¹⁶⁷



There has been some controversy in the literature over the structure of the products obtained from the reaction of thioureas with acetylenic

²⁹⁶ V. M. Fedoseev and V. S. Churilin, *Zh. Org. Khim.* **8**, 205 (1972).

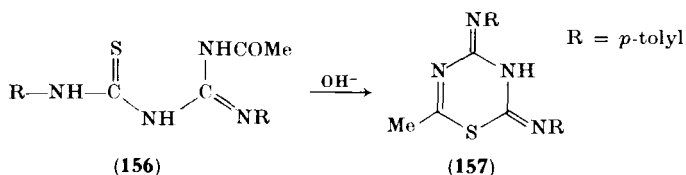
²⁹⁷ M. Tišler, *Tetrahedron Lett.*, 12 (1959).

²⁹⁸ M. Tišler, *Arch. Pharm. (Weinheim)* **293/65**, 621 (1960).

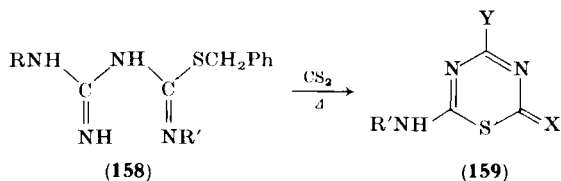
esters. The vast majority of papers, even in the more recent literature, have referred to these products as 1,3-thiazines. The latest evidence indicates, however, that these products are actually iminothiazolidinones¹⁵⁶ (see Section III, B, 1).

2. Two Nitrogen Atoms and One Sulfur Atom

Only one kind of six-membered ring system containing two nitrogens and one sulfur has been prepared from thiourea-type starting materials, namely 1,3,5-thiadiazines. The first report of this sort of preparation is that of Fromm and Weller,⁶⁵ who in 1908 found that the thiourea



156 cyclizes under the influence of alkali to give **157**. A more general process has recently been exploited by Dhake^{266,299} to prepare compounds of type **159** (X = S, Y = NHR₁) by treatment of the 1-amidino-2-thiopseudoureas **158** with carbon disulfide. The thiadiazine products **159** are favored at short reaction times, but *s*-triazines are



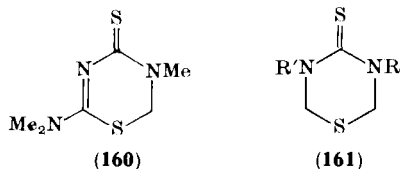
produced on prolonged heating of the mixture. Compounds of type **159** (X = S, Y = Me₂N) may also be prepared by treating amidinothiureas with thiophosgene in the presence of triethyl amine.³⁰⁰ Products of structure **159** (X = O, Y = Me₂N) may also be gained by treatment of amidinothiureas with 1,1'-carbonyldiimidazole.³⁰¹ Another procedure leading to similar products is the treatment of 2-methyl-2,4-dithiopseudobiurets with phosgene to give **159** (X = O, Y = SMe), with thiophosgene to give **159** (X = S, Y = SMe), or with *p*-toluenesulfonylcarbonimidoyl dichloride to give **159** (X = N-*p*-tolyl, Y = SMe).⁸³

²⁹⁹ J. D. Dhake, *Indian J. Chem.* **9**, 1415 (1971).

³⁰⁰ J. E. Oliver and A. B. DeMilo, *J. Heterocycl. Chem.* **8**, 1087 (1971).

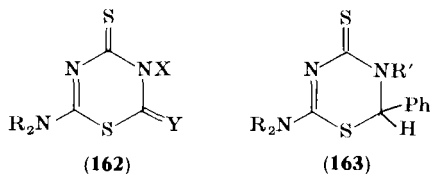
³⁰¹ J. E. Oliver, B. A. Bierl, and J. M. Ruth, *J. Org. Chem.* **37**, 131 (1972).

Formaldehyde has been employed to prepare analogs of **159** with a higher degree of saturation. Thus **160** may be made by treating 1,1,5-trimethyl-2,4-dithiobiuret with refluxing aqueous formaldehyde,¹⁹⁷ and



the series **161** is formed on treatment of disubstituted thioureas with formaldehyde in the presence of hydrogen sulfide.³⁰²

A very useful preparation of 1,3,5-thiadiazine type rings involves the report of Goerdeler and Lüdke¹⁶⁷ that **154** undergoes reaction with phenyl isocyanate to give **162** (X = Ph, Y = O) and with carbodiimides to give **162** (X = R', Y = NR'). Other compounds **163** may be prepared by treatment of **154** with benzaldehyde imines,¹⁶⁷ a process which was also recently utilized by Kristian *et al.*³⁰³



Less useful preparations of 1,3,5-thiadiazines in which they are formed as components of mixtures include that of Chase and Walker.²⁶² They isolated a thiadiazine as a product of the reaction of thiourea, bromine, and *p*-chlorophenylacetonitrile in acetone. The function of the nitrile, which was not incorporated into the product, is not apparent. The product of a similar reaction, without the nitrile, was assigned a dithiazine structure by Baumann.³⁰⁴ Oliver and Stokes²⁰² also reported that a 1,3,5-thiadiazine is formed among the myriad of identified products of the 15-month air oxidation of 1,1,5,5-tetramethyl-2,4-dithiobiuret.

3. One Nitrogen Atom and Two Sulfur Atoms

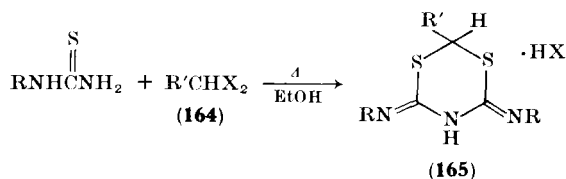
The dihydro-1,3,5-dithiazine ring system **165** can be prepared by treatment of thiourea or monosubstituted thioureas with geminal

³⁰² M. C. Seidel and F. E. Boettner, *J. Heterocycl. Chem.* **9**, 231 (1972).

³⁰³ P. Kristian, D. Koscik, and J. Bernat, *Chem. Zvesti* **27**, 280 (1973); *Chem. Abstr.* **79**, 53271 (1973).

³⁰⁴ E. Baumann, *Ber.* **18**, 883 (1885).

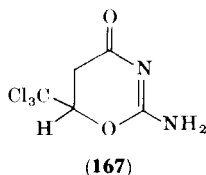
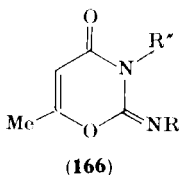
dihalides (**164**). The halides are usually unsubstituted ($R' = H$); however, one report using phenyldihalo- or methyldihalomethanes has appeared.¹⁶ The halogen (X) of **165** may be chlorine,¹⁶ bromine,^{16,305} or iodine.^{16,305,306}



C. NITROGEN- AND OXYGEN-CONTAINING RINGS

1. One Nitrogen Atom and One Oxygen Atom

The preparation of dihydro-4*H*-1,3-oxazinones (**166**) from mono-^{239,240} or disubstituted³⁰⁷ thiopseudoureas has been accomplished by their reaction with diketene. In one case,²³⁹ a 2-alkylthio intermediate in the



formation of **166** was isolated at low temperatures. At higher temperatures, **166**, resulting from elimination of thiol from the intermediate, was obtained along with some pyrimidine side product.

Luknitskii *et al.*²⁴⁵ prepared **167** by treatment of a thiopseudourea with 4-trichloromethyl-2-oxetanone (**111**). Interestingly, beginning with a selenopseudourea in this reaction, the product is the 1,3-selenazine analog of **167**,²⁴⁵ having resulted from loss of the elements of ROH rather than RSeH as would have been expected from the example leading to **167**.

In a different synthesis of the 1,3-oxazine ring system, Ignatova *et al.*³⁰⁸ reported preparation of **170** in yields of 70–93% by the reaction of

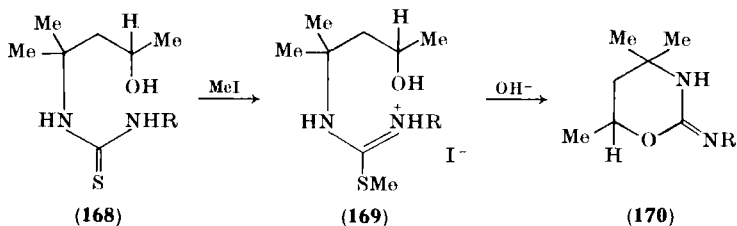
³⁰⁵ C. H. Grogan and L. M. Rice, *J. Org. Chem.* **28**, 2486 (1963).

³⁰⁶ G. T. Esayan and E. E. Oganessian, *Dokl. Akad. Nauk Arm. SSR* **31**, 87 (1960); *Chem. Abstr.* **55**, 10466i (1961).

³⁰⁷ R. N. Lacey, *J. Chem. Soc.*, 845 (1954).

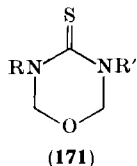
³⁰⁸ L. A. Ignatova, P. L. Ovechkin, M. Z. Branzburg, A. Ye. Gekhman, and B. V. Unkovskii, *Khim. Geterotsikl. Soedin.*, 1037 (1972).

the hydroxypropyl thiourea **168** with iodomethane followed by treatment of the intermediate thiopseudourea **169** with alkali.



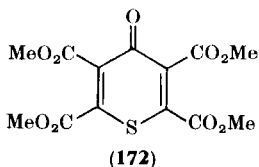
2. Two Nitrogen Atoms and One Oxygen Atom

The only preparation of a ring system of this type from thioureas, which has been reported in the literature, is the tetrahydro-1,3,5-oxadiazine series of Seidel and Boettner,³⁰² who synthesized compounds **171** by treating thioureas with formaldehyde in the presence of *p*-toluenesulfonic acid.



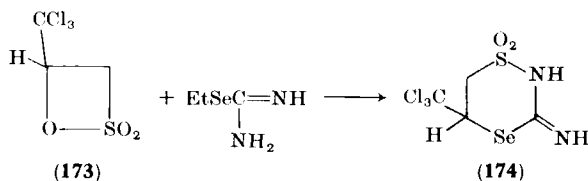
D. MISCELLANEOUS SIX-MEMBERED RINGS

A recent report of Winterfeldt²¹⁴ indicated that 2,3,5,6-tetracarbo-methoxy-4*H*-thiin-4-one (**172**) is obtained, among other products, when 1,1,3,3-tetramethyl-2-thiourea is treated with dimethyl acetylenedicarboxylate.



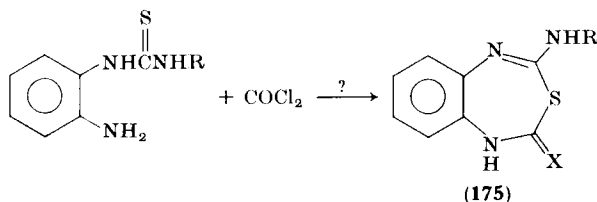
Perhaps the most unusual six-membered ring compound prepared from a thiourea analog is to be found in the report of Luknitskii *et al.*,²⁴⁸ who treated 2-ethyl-2-selenopseudourea with the trichloromethyl

sultone **173** to give the novel tetrahydro-1,4,2-thiaselenazine-1,1-dioxide **174**.



V. Seven-Membered Rings

The literature of seven-membered ring heterocycles prepared from thioureas is very limited, and some of the structural assignments that have been made are open to serious question. Ghosh³⁰⁹ proposed that the reaction between 1-(2-aminophenyl)-3-substituted-2-thioureas and α -bromoacetophenone produced 2-bromomethyl-3,1,5-benzothiadiazepines. Pathak,³¹⁰ in refuting the structure proposed by Ghosh, asserted that the product could not contain bromine, but his alternative structures are somewhat tenuous. In view of other work, Ghosh's product could be a 2-imino-4-thiazoline derivative of the thiourea (see Section III, B, 1). Ghosh³⁰⁹ proposed structure **175** (X = O) for the reaction product between a 1-(2-aminophenyl)-2-thiourea and phosgene,

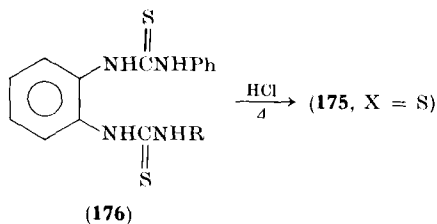


although more recent work suggests that the product could be a 1,3-thiazetidin-4-one (one possibility is **6**, Ar = 2-aminophenyl, Ar' = R, X = O) formed only from the thiourea portion of the molecule. Ghosh and Guha³¹¹ reported a series of ring closure reactions of *o*-phenylenebisthioureas (**176**) to form the 1,2-dihydro-3,1,5-benzothiadiazepine-2-thiones (**175**, X = S). In the case of the corresponding *o*-phenylenethiourea-ureas, the products were considered to be tetrahydro-1,3,5-benzotriazepines if R was an aryl group or dihydro-3,1,5-benzothiadiazepines if R was allyl or methyl.³¹¹

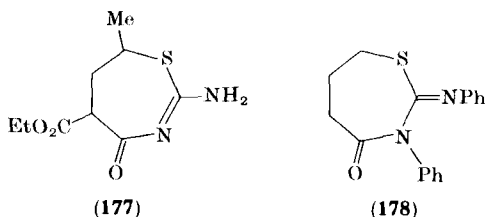
³⁰⁹ T. N. Ghosh, *J. Indian Chem. Soc.* **8**, 71 (1931).

³¹⁰ K. B. Pathak, *J. Indian Chem. Soc.* **12**, 463 (1935).

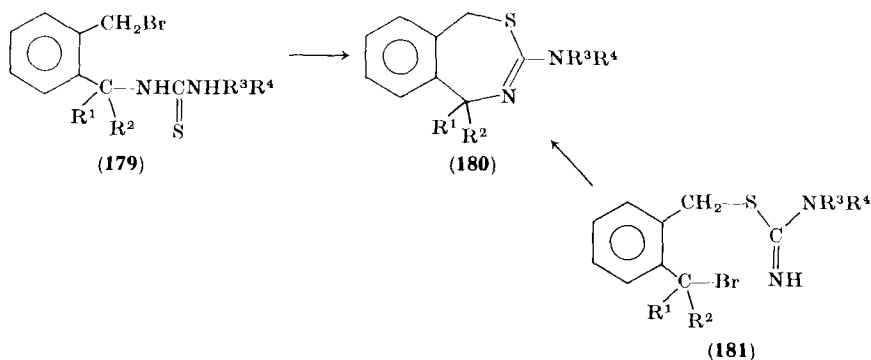
³¹¹ T. N. Ghosh and P. C. Guha, *J. Indian Chem. Soc.* **6**, 181 (1929).



Johnson and Hill,³¹² on attempting to synthesize 5-allyl-2-thio-barbituric acid, reported formation of the 2-amino-4,5,6,7-tetrahydro-1,3-thiazepin-4-one **177** from the reaction of thiourea with allyldiethylmalonate.



1,3-Diphenyl-2-thiourea, when heated under reflux in acetone with 4-bromobutanoyl chloride, was reported by Reinhoudt²¹² to give a 19% yield of 2-phenylimino-3-phenylperhydro-1,3-thiazepin-4-one (**178**). In addition, cyclization of the thiourea **179** gave the disubstituted 3-amino-1*H*,5*H*-2,4-benzothiazepin-5-one (**180**; $R^1R^2 = O$). Other derivatives (**180**; $R^1 = R^2 = H$, or $R^1R^2 = O$; $R^3 = R^4 = CH_3$) could be prepared via cyclization of the thiopseudoureas **181**. In this case, if R^3 was phenyl and R^4 was hydrogen, then the product was a 2-phenylimino modification of **180**.²¹²

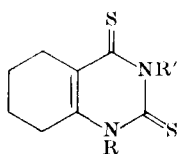


³¹² T. B. Johnson and A. J. Hill, *Amer. Chem. J.* **45**, 356 (1911).

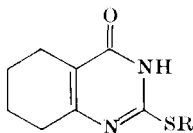
VI. Heteropolycyclic Rings

A. QUINAZOLINES

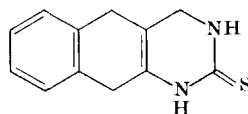
Cyclohexanones have been employed in reactions with thioureas to give quinazolines with varying degrees of saturation. For example, octahydroquinazolinedithiones (**182**) have been prepared from cyclohexanone and symmetrical³¹³⁻³¹⁵ or unsymmetrical³¹⁴ disubstituted



(182)

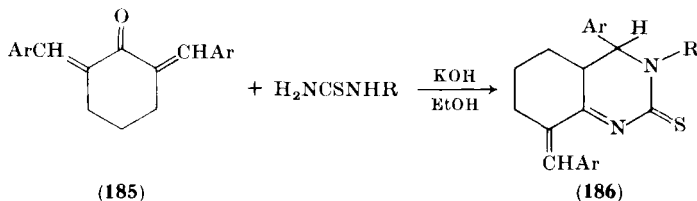


(183)



(184)

thioureas. Similar compounds can be obtained from 2-carbalkoxycyclohexanones and thiourea to give **183** ($R = H$) or with a thiopseudourea to give **183** ($R = Me$),³¹⁶ a process which has been extended to produce the benz[*g*]hexahydroquinazoline **184**.³¹⁷ A similar product is formed when thioureas are heated with 2-carbethoxy-1-aminocyclohexene.³¹³ A more unusual leaving group was employed by Zigeuner *et al.*,³¹⁸ who prepared an octahydroquinazoline by treating 2-(*N,N*-dimethylamino-methyl)cyclohexanone with thiourea in methanolic sodium methoxide. Another series of octahydroquinazolines (**186**) was synthesized by Sammour *et al.*,³¹⁹ who treated the bisarylidene cyclohexanone **185** with various thioureas in ethanolic potassium hydroxide.



(185)

(186)

³¹³ J. Schoen, *Rocz. Chem.* **29**, 549 (1955).

³¹⁴ J. Schoen, *Rocz. Chem.* **35**, 967 (1961).

³¹⁵ J. Schoen and K. Bogdanowicz, *Rocz. Chem.* **36**, 1493 (1962).

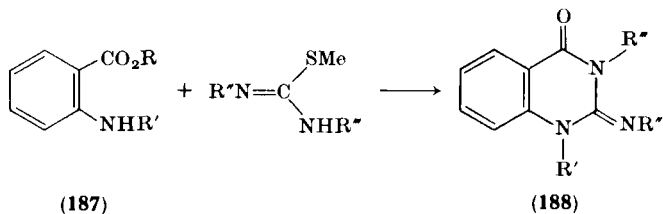
³¹⁶ F. H. S. Curd, D. N. Richardson, and F. L. Rose, *J. Chem. Soc.*, 378 (1946).

³¹⁷ A. Rosowsky, E. P. Burrows, P. C. Huang, and E. J. Modest, *J. Heterocycl. Chem.* **9**, 1239 (1972).

³¹⁸ G. Zigeuner, V. Eisenreich, and W. Immel, *Monatsh. Chem.* **101**, 1745 (1970).

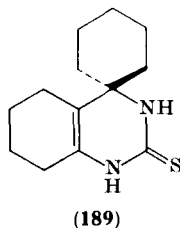
³¹⁹ A. Sammour, A. Marei, and M. H. M. Hussein, *U.A.R. J. Chem.* **12**, 451 (1969); *Chem. Abstr.* **74**, 53702 (1971).

Many workers have employed anthranilic acid derivatives (**187**) to prepare tetrahydroquinazolines. Thus Deck and Dains³²⁰ synthesized a series of tetrahydroiminoquinazolinones (**188**) by conducting the reaction with 2-thiopseudoureas in refluxing xylene, and two other groups of workers^{321,322} prepared **188** ($R' = H$, $R'' = Ph$, $R''' = H$).



Isatoic anhydrides have recently been employed^{323,324} as anthranilic acid analogs to prepare additional compounds in the series. Similarly an intramolecular cyclization of 1-(2-cyanophenyl)-3-phenyl-2-thiourea, an anthranilonitrile derivative, was employed by Taylor and Ravindranathan³²⁵ to give an iminotetrahydroquinazoline. A similar process was studied by Söderbaum and Widman^{326,327} in the intramolecular cyclization of 2-(3'-phenylthiureido)benzyl alcohol to give tetrahydroquinazolines. A series of unique quinazolines containing 1-hydroxyl substituents were also reported as resulting from *N*-hydroxythiourea derivatives of anthranilate esters.³²⁸

Spiroquinazolines have been synthesized by two groups. Gawlowski and Mirek³²⁹ recently reported the preparation of **189** from cyclo-



³²⁰ J. F. Deck and F. B. Dains, *J. Amer. Chem. Soc.* **55**, 4986 (1933).

³²¹ H. L. Wheeler, T. B. Johnson, D. F. McFarland, *J. Amer. Chem. Soc.* **25**, 787 (1903).

³²² N. A. Lange and F. E. Sheibley, *J. Amer. Chem. Soc.* **54**, 1994 (1932).

³²³ Th. Kappe, W. Steiger, and E. Ziegler, *Montash. Chem.* **98**, 214 (1967).

³²⁴ E. Ziegler, W. Steiger, and Th. Kappe, *Monatsh. Chem.* **99**, 1499 (1968).

³²⁵ E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.* **27**, 2622 (1962).

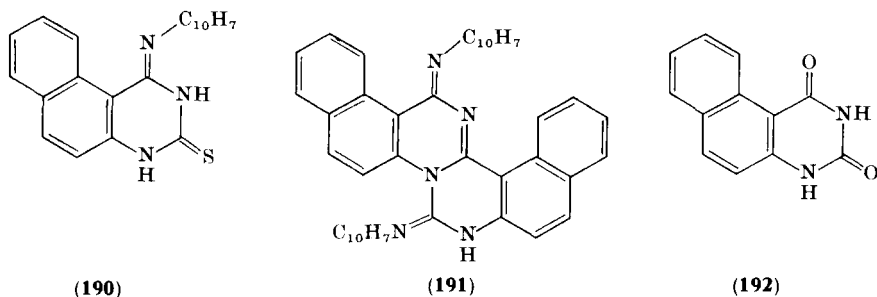
³²⁶ H. G. Söderbaum and O. Widman, *Ber.* **22**, 1665 (1889).

³²⁷ H. G. Söderbaum and O. Widman, *Ber.* **22**, 2933 (1889).

³²⁸ R. Stoffel and H.-J. Bresse, *Arch. Pharm. (Weinheim)* **306**, 579 (1973).

hexanone and thiourea under acidic conditions; similar results could be obtained beginning with 2-cyclohexylidenecyclohexanone^{329,330} or with 2-(1-chlorocyclohexyl)cyclohexanone.³²⁹ Also, the thiourea may be monosubstituted,³³⁰ in which case 1-substituted spiroquinazolines (189) are obtained.

The most unusual preparation of quinazolines from thioureas is that of Dziewoński *et al.*,³³¹ who fused β -naphthylamine and thiourea to give two products, the structures of which they suggested were **190** and **191** on the basis of elemental analyses and hydrolysis of the reaction



mixture to give solely 1,2,3,4-tetrahydrobenzo[*f*]quinazoline-2,4-dione (192); however, the hydrolysis of **191** to give **192** under these conditions is questionable.

B. 4-AMINOQUINOLINES

A useful preparation for heterocycles which has been perfected by Moszew, Dziewoński, and Schoen, and co-workers, and which has received only scant attention in heterocyclic compendia,³³² involves the fusion of 1-aryl-2-thioureas containing a proton on the 1-nitrogen atom and aldehydes or ketones with α -hydrogen atoms at 150–300° to give 4-aminoquinolines. For example, Moszew³³³ reported that reaction of acetophenone (193) and 1,3-diphenyl-2-thiourea (194) gives 4-anilino-2-phenylquinoline (195) and a quinolinoquinoline product. Various

³²⁹ J. P. Gawlowski and J. Mirek, *Rocz. Chem.* **46**, 421 (1972).

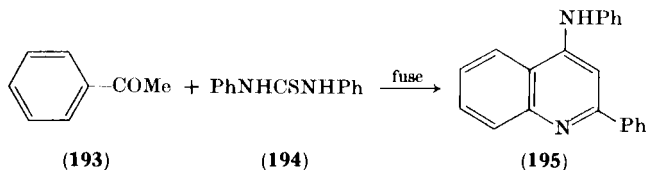
³³⁰ G. Jaenecke, *Z. Chem.* **8**, 383 (1968).

³³¹ K. Dziewoński, L. Sternbach, and A. Strauchen, *Rocz. Chem.* **17**, 1 (1937).

³³² J. V. Crawford and E. R. Webster, in "Six-Membered Heterocyclic Nitrogen Compounds with Four Condensed Rings" (C. F. H. Allen, ed.), pp. 114–115. Wiley (Interscience), New York, 1951.

³³³ J. Moszew, *Bull. Int. Acad. Pol. Sci., Classe Sci. Math. Nat.* **A1938**, 98 (1938); *Chem. Abstr.* **33**, 4987 (1939).

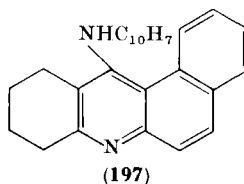
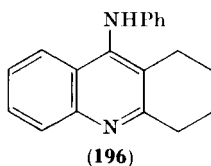
methylated isomers of **195** were prepared using methyl-substituted acetophenones^{334,335} and/or (methylphenyl)thioureas.³³⁴⁻³³⁷ Naphthylthioureas react with acetophenones to give benzo[*f*]quinolines,³³⁴ and



other substituents have included chloro on either or both reactants.³³⁷ Other carbonyl containing reactants which have been reported are methyl 2,2-diphenylethyl ketone,³³⁸ 5,6,7,8-tetrahydro-2-acetylnaphthalene,³³⁹ and phenylacetaldehyde,³⁴⁰ which react with **194** to give 4-anilino-2-(2,2-diphenylethyl)quinoline, 4-anilino-2-(2'-tetralyl)quinoline, and 4-anilino-3-phenylquinoline, respectively. In a special case,³³⁶ deoxybenzoin, although lacking a carbonyl group, undergoes reaction with **194** to give 4-anilino-2,3-diphenylquinoline.

The mechanism of these reactions has been suggested to involve initial decomposition of the thiourea to isothiocyanate and amine, and the latter reacts with the carbonyl compound to form a Schiff's base. Condensation of the Schiff's base with the isothiocyanate present, followed by loss of H_2S gives the observed products.^{336,338,340}

The carbonyl-containing reactant may be cyclic, in which case the products are fused quinolines. Thus if cyclohexanone reacts with **194**, the product is the tetrahydroacridine **196**,^{313,341} or with 1,3-di-2-



³³⁴ K. Dziewoński, L. Gizler, and J. Moszew, *Rocz. Chem.* **15**, 400 (1935); *Chem. Abstr.* **30**, 1378⁴ (1936).

³³⁵ K. Dziewoński and J. Moszew, *Bull. Int. Acad. Pol. Sci., Classe Sci. Math. Nat.* **A1936**, 258 (1936); *Chem. Abstr.* **31**, 1812 (1937).

³³⁶ K. Dziewoński and J. Moszew, *Rocz. Chem.* **14**, 1123 (1934).

³³⁷ K. Dziewoński and J. Mayer, *Rocz. Chem.* **14**, 1157 (1934).

³³⁸ J. Moszew and W. Zankowska-Jasińska, *Rocz. Chem.* **29**, 541 (1955).

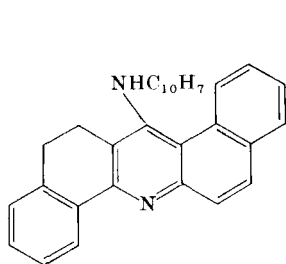
³³⁹ J. Moszew and M. Bala, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **12**, 393 (1964).

³⁴⁰ J. Moszew and H. Famielcówna, *Rocz. Chem.* **22**, 80 (1948).

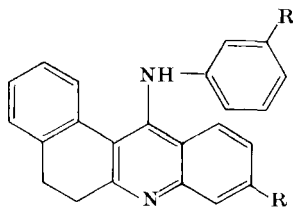
³⁴¹ K. Dziewoński and J. Schoen, *Bull. Int. Acad. Pol. Sci., Classe Sci. Math. Nat.* **1934A**, 448 (1934); *Chem. Abstr.* **29**, 2958 (1935).

naphthyl-2-thiourea, cyclohexanone gives 12-(2-naphthylamino)-8,9,10,11-tetrahydrobenz[*a*]acridine (**197**).³⁴²

α -Tetralone has been utilized in these reactions with 1,3-diphenyl-2-thioureas^{315,341} to give dihydrobenz[*c*]acridines and with 1,3-di-2-naphthyl-2-thiourea³⁴² to produce a dihydrodibenz[*a,h*]acridine (**198**).



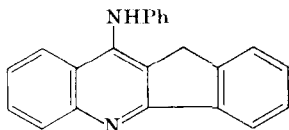
(198)



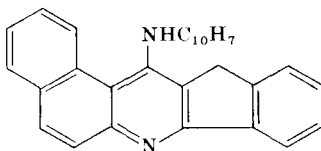
(199)

β -Tetralone gives with **194**,³⁴³ or with 1,3-di-*m*-tolyl-2-thiourea,³⁴⁴ dihydrobenz[*a*]acridines (**199**, R = H, Me); this ketone, on reaction with 1,3-di-2-naphthyl-2-thiourea, gives a dihydrodibenz[*a,j*]acridine.³⁴³

A ketone contained in a five-membered ring was also employed in these reactions when α -indanone was fused with **194** to give the indeno[3,2-*b*]quinoline **200**³⁴⁵ and with 1,3-di-2-naphthyl-2-thiourea to give the indeno[3,2-*b*]-1-azaphenanthrene **201**.



(200)



(201)

These reactions provide an important entry into the benzazine series. The parent rings can be prepared from the products obtained by hydrolysis and dehydrogenation over zinc dust.^{338,344,346} The simplicity of the procedure is an attractive feature even though some of the fusion reactions proceed in poor yield.

³⁴² J. Schoen and K. Bogdanowicz, *Rocz. Chem.* **34**, 1339 (1960).

³⁴³ J. Schoen and W. Laskowska, *Rocz. Chem.* **39**, 1633 (1965).

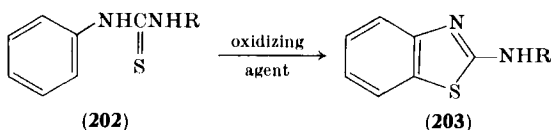
³⁴⁴ J. Schoen and W. Laskowska, *Rocz. Chem.* **40**, 1315 (1966).

³⁴⁵ K. Dziewoński, J. Schoen, S. Ochab, and K. Bogdanowicz, *Rocz. Chem.* **37**, 561 (1963).

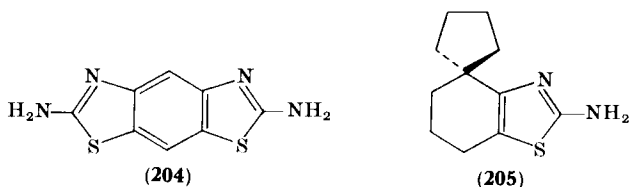
³⁴⁶ J. Schoen and K. Bogdanowicz, *Rocz. Chem.* **36**, 445 (1962).

C. BENZO- AND NAPHTHO-FUSED FIVE- AND SIX-MEMBERED HETEROCYCLIC RINGS

1-Aryl-2-thioureas (**202**) are an important source of aromatic fused-ring compounds. By far the most frequently encountered conversion of **202** to the latter are those leading to 2-aminobenzo[*d*]thiazoles (**203**),



formed by treatment of the thioureas with oxidizing agents. Sprague and Land⁷⁵ provided a comprehensive survey of these reactions, covering the literature through 1957, involving oxidation with bromine, sulfonyl chloride, sulfur monochloride, and chlorine. Other oxidants which have been employed are thionyl chloride³⁴⁷ and sulfur in conjunction with aromatic amines.³⁴⁸ Reports, including those subsequent to 1957, which do not present novel uses of the above reactions will be omitted. Other variations of these reactions have included the formation of compounds of type **203** from bis(arylamidino) disulfides³⁴⁹ and 2-(2-aminophenyl)thiopseudoureas.³⁵⁰ The same product types **203** have been obtained on oxidation of dithiobiurets³⁵¹ or dithiopseudobiurets³⁵²⁻³⁵⁴ with bromine,^{351,352,354} or iodine.^{353,354} An interesting product utilizing this reaction type has resulted from treatment of *m*-phenylenebis-(thiourea) with bromine giving the benzo[1,2-*d*:5,4-*d'*]bisthiazole **204**.³⁵⁵



³⁴⁷ Y. Iwakura and K. Kurita, *Bull. Chem. Soc. Jap.* **43**, 2535 (1970).

³⁴⁸ T. G. Levi, *Atti Congr. Naz. Chim. Ind.*, 400 (1924); *Chem. Abstr.* **19**, 1411 (1925).

³⁴⁹ G. Barnikow and J. Bödeker, *Chem. Ber.* **100**, 1394 (1967).

³⁵⁰ F. Kurzer and P. M. Sanderson, *J. Chem. Soc.*, 230 (1962).

³⁵¹ M. G. Paranjpe, *Indian J. Chem.* **6**, 132 (1968).

³⁵² S. N. Dixit, *J. Indian Chem. Soc.* **40**, 153 (1963); *Chem. Abstr.* **59**, 8752c (1963).

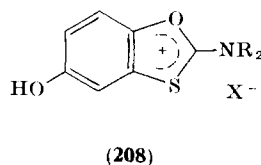
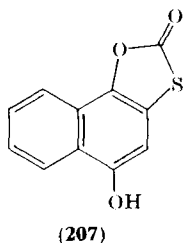
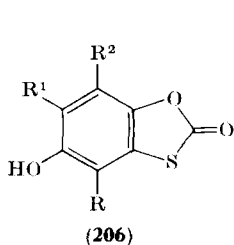
³⁵³ V. K. Verma, *Indian J. Chem.* **1**, 300 (1963).

³⁵⁴ C. P. Joshua, *J. Indian Chem. Soc.* **38**, 155 (1961).

³⁵⁵ G. Barnikow, H. Kunzek, and M. Hofmann, *J. Prakt. Chem.* **27**, 271 (1965).

A tetrahydrospirobenzothiazole **205** was produced in a different reaction type when an α -bromospiroketone was treated with thiourea.³⁵⁶ Similarly, tetrahydrobenzothiazoles are formed when 6-bromo-2-carboethoxycyclohexanone reacts with monosubstituted thioureas,³⁵⁷ or when 2-chlorocyclohexanone is treated with 1,3-disubstituted thioureas.³⁵⁸

Lau and Gompf³⁵⁹ prepared a series of 2-amino-6-hydroxybenzo[*d*]-thiazoles and corresponding naphtho[1,2-*d*]thiazoles on treating 1,4-benzoquinone and 1,4-naphthoquinone with thiourea in acidic media at room temperature. At high temperature the products of the reaction with 1,4-benzoquinone are 5-hydroxybenz[*d*]-1,3-oxathiol-2-ones **206**.³⁵⁹⁻³⁶¹ With 1,4-naphthoquinones, the corresponding naphtho[2,1-*d*]-1,3-oxathiol-2-ones **207** are formed,³⁶² whereas, with tetra-substituted thioureas and 1,4-benzoquinone, the benz[*d*]oxathiolium salts **208** are produced.^{363,364}



Benzimidazoles are obtained when thioureas are treated with *o*-phenylenediamine.^{320,365,366} Also a benzimidazole product **209** is formed when 1-(2-aminophenyl)-3-phenyl-2-thiourea (**210**) is oxidized with mercury(II) chloride,³⁶⁷ or is heated in hydrochloric acid.³¹¹ Matsui *et al.*³⁶⁸ have recently found that 2-aminobenzimidazoles are produced

³⁵⁶ A. N. Nesmeyanov, K. A. Pecherskaya, and T. P. Tolstaya, *Uch. Zap. Mosk. Gos. Univ. Im. M. V. Lomonosova* No. 132, *Org. Khim.* **7**, 66 (1950); *Chem. Abstr.* **49**, 3853d (1955).

³⁵⁷ P. H. L. Wei, U.S. Patent 3,694,450 (1972); *Chem. Abstr.* **78**, 16173 (1973).

³⁵⁸ G. de Stevens, H. A. Luts, and A. Halamandaris, *J. Org. Chem.* **23**, 114 (1953).

³⁵⁹ P. T. S. Lau and T. E. Gompf, *J. Org. Chem.* **35**, 4103 (1970).

³⁶⁰ H. Burton and S. B. David, *J. Chem. Soc.*, 2193 (1952).

³⁶¹ P. T. S. Lau and M. Kestner, *J. Org. Chem.* **33**, 4426 (1968).

³⁶² D. E. Thurman and H. W. Stollings, *J. Heterocycl. Chem.* **10**, 117 (1973).

³⁶³ H. Hartmann, D.D.R. Patent 80,220 (1971); *Chem. Abstr.* **75**, 35994 (1971).

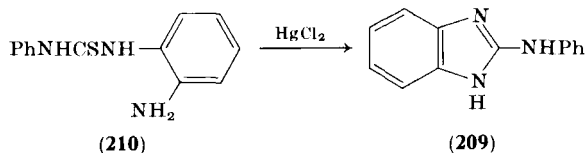
³⁶⁴ H. Hartmann, *Z. Chem.* **11**, 381 (1971).

³⁶⁵ A. R. Todd, F. Bergel, and Karimullah, *Ber.* **69**, 217 (1936).

³⁶⁶ O. Kym, *J. Prakt. Chem.* **75**, 323 (1907).

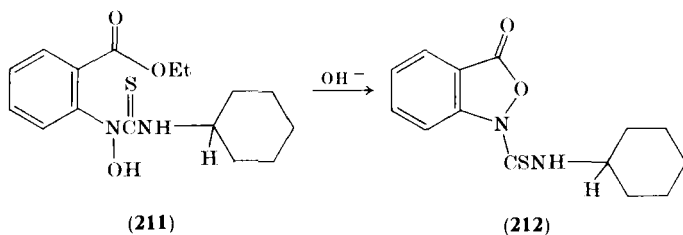
³⁶⁷ A. Mohsen and M. E. Omar, *Pharmazie* **27**, 798 (1972); *Chem. Abstr.* **78**, 72005p (1973).

when 1-(2-aminophenyl)-3-carbethoxy-2-thiourea is heated in strongly protic solvents, or when 1,2-bis(3-carbethoxy-2-thiureido)benzene is treated with heavy metal ions or with alkaline hydrogen peroxide. Benzimidazolinones may be formed on treatment of 1,3-diaryl-2-thioureas with sodium peroxide.^{369,370} Other products reported by Ghosh from reaction of **210** with FeCl_3 or with nitrous acid were claimed to be 2,1,4-benzothiadiazines³¹¹ and benzotriazoles,³⁰⁹ respectively.



Fused oxygen and nitrogen-containing rings may also be prepared in reactions with thioureas; thus, dihydrobenzoxazine products are obtained on treatment of salicyloyl chloride with thioureas³⁷¹ or on fusion of salicylate esters with thiopseudoureas.³²⁰ When the thiopseudoureas are treated with *o*-aminophenol, the products are benzoxazoles.³²⁰ A naphthyl analog of a benzoxazole is produced on treatment of 1-(2-hydroxy-1-naphthyl)-2-thiourea with dimethyl sulfate.³⁷²

Stoffel and Bresse³²⁸ have found that the cyclohexyl-*N*-hydroxythiourea derivative of anthranilic acid **211** undergoes cyclization in base to give the dihydrobenz[*c*]isoxazolone compound **212**. With substituents other than cyclohexyl, however, the products of the reaction are quinazolines (see above).



³⁶⁸ T. Matsui, M. Nagano, J. Tobitsuka, and K. Oyamada, *J. Pharm. Soc. Jap.* **93**, 977 (1973).

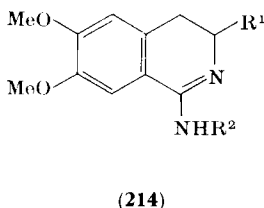
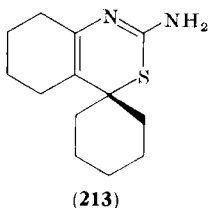
³⁶⁹ J. Shibasaki, T. Koizumi, and S. Matsumura, *Yakugaku Zasshi* **88**, 491 (1968).

³⁷⁰ J. Shibasaki, T. Koizumi, and S. Matsumura, *Yakugaku Zasshi* **88**, 499 (1968).

³⁷¹ E. Ziegler, G. Kollenz, and Th. Kappe, *Monatsh. Chem.* **100**, 540 (1969).

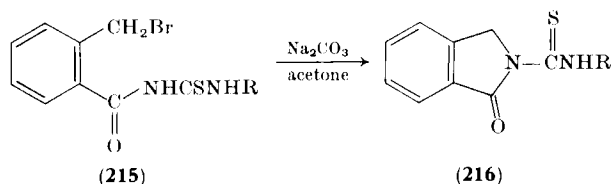
³⁷² B. Arventiev, M. Strul, H. Wexler, and D. Cahane, *Acad. Repub. Pop. Rom. Filiala Iasi Stud. Cercet. Stiint. Chim.* **7**, 25 (1956); *Chem. Abstr.* **53**, 8083i (1959).

A six-membered nitrogen-sulfur heterocycle, namely, a 2,3-dihydro-2-imino-4*H*-benzo[*e*]thiazin-4-one, is produced on reaction of methyl 2-chloro-3,5-dinitrobenzoate with thiourea in basic medium;³⁷³ furthermore, a tetrahydrospirobenzothiazine **213** is formed in addition to its hexahydrospiroquinazoline analog on interaction of cyclohexanone with thiourea in hydrochloric acid.³²⁹



Hazzaa *et al.*³⁷⁴ recently reported formation of a series of 3,4-dihydro-6,7-dimethoxyisoquinolines (**214**) on treatment of dimethoxyphenethylthioureas with phosphoryl chloride followed by oxidation with mercury(II) chloride.

Another use of a thiourea to prepare a benzo-fused ring system is that of Reinhoudt,²¹² who treated the 1-(2-bromomethylbenzoyl)-2-thioureas **215** with sodium carbonate in acetone to give the isoindolin-1-ones **216**.



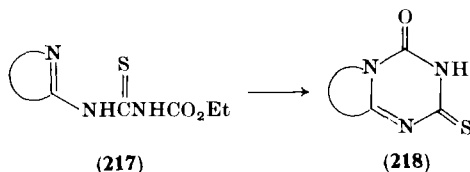
D. MISCELLANEOUS HETEROCYCLES

A simple preparation of otherwise difficulty prepared heterocyclic ring systems is the cyclization of derivatives of type **217**, resulting from reaction of carbethoxy isothiocyanate with 2-aminoazaheterocycles to give bridgehead-nitrogen heterobicyclic *s*-triazinonethiones **218**. The hetero-rings of **217** which have been reported in this reaction are

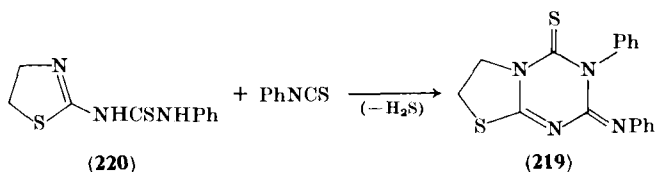
³⁷³ D. S. Deorha and S. P. Sareen, *J. Indian Chem. Soc.* **42**, 97 (1965).

³⁷⁴ A. A. B. Hazzaa, A. M. M. E. Omar, and M. E. Ragab, *Pharmazie* **28**, 364 (1973.)

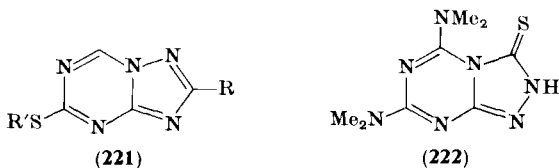
³⁷⁵ L. Capuano and H. J. Schrepfer, *Chem. Ber.* **104**, 3039 (1971).



3-pyrazolyl,³⁷⁵ 3-(1,2,4-triazolyl),³⁷⁶⁻³⁷⁸ 2-thiazolyl,³⁷⁹⁻³⁸¹ 2-pyridyl,³⁸² and 3-pyridazyl.³⁸³ A product similar to these, 2,3,6,7-tetrahydro-3-phenyl-2-phenyliminothiazolo[3,2-*a*]-*s*-triazine-4-thione (219), was reported by Klayman and Milne³⁸⁴ to arise when 1-phenyl-3-(2-thiazolin-2-yl)-2-thiourea (220) was treated with phenyl isothiocyanate.



[1,2,4]-Triazolo[2,3-*a*]-*s*-triazines (221) were prepared by Bokaldere *et al.*³⁸⁵ by treating 1-(1,2,4-triazol-3-yl)-2-thiopseudoureas with triethyl orthoformate. The isomeric ring system [1,2,4]-triazolo[4,3-*a*]-*s*-triazine (222) was reported by DeMilo *et al.*³⁸⁶ to arise when the thiourea-



³⁷⁶ A. De Milo, 8th Middle Atlantic Regional Meeting, Amer. Chem. Soc., Org. Div. Jan. 17, 1973.

³⁷⁷ T. Hirata, J. M. Tranmoh, H. B. Wood, A. Goldin, and J. S. Driscoll, *J. Heterocycl. Chem.* **9**, 99 (1972).

³⁷⁸ R. P. Bokaldere and A. Ya. Liepin, *Khim. Geterotsikl. Soedin.*, 276 (1973).

³⁷⁹ M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* **21**, 74 (1973).

³⁸⁰ M. Nagano, J. Tobitsuka, T. Matsui, and K. Oyamada, *Chem. Pharm. Bull.* **20**, 2618 (1972).

³⁸¹ M. Nagano, T. Matsui, J. Tobitsuka, and K. Oyamada, *Chem. Pharm. Bull.* **20**, 2626 (1972).

³⁸² B. Stanovnik and M. Tišler, *Synthesis*, 308 (1972).

³⁸³ M. Zupan, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **37**, 2960 (1972).

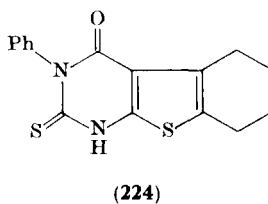
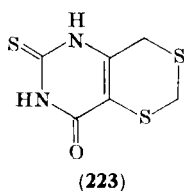
³⁸⁴ D. L. Klayman and G. W. A. Milne, *Tetrahedron* **25**, 191 (1969).

³⁸⁵ R. P. Bokaldere, A. Ya. Liepin, I. B. Mazheika, I. S. Yankovska, and E. E. Liepin'sh, *Khim. Geterotsikl. Soedin.*, 419 (1973).

³⁸⁶ A. B. DeMilo, J. E. Oliver, and R. D. Gilardi, *J. Heterocycl. Chem.* **10**, 231 (1973).

like compound, 1,1'-thiocarbonyldiimidazole, reacted with a triazinyl-hydrazine compound.

A myriad of types of fused-ring pyrimidines derived from thioureas have been reported in the literature. For example, Howard and Lindsey³⁸⁷ reported the [1,3]-dithiino[5,4-*d*]pyrimidine ring system **223**, and other workers made the octahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine **224** in 90% yield.³⁸⁸ The formation of both of these products was via a base-promoted condensation of a thiourea with a carbethoxy group; however, in the former case the reaction was intermolecular and in the latter, intramolecular. Other unusual fused systems of this type have



included the indeno[3,2-*d*],^{389,390} oxino[3,2-*d*],³⁹¹ pyrimidino[4,5-*d*],³⁹² imidazo[4,5-*e*],³⁹³ and pyrimidino[2',1':2,3]-[1,3]thiazino[5,6-*d*]³⁹⁴ pyrimidinonethione rings.

Several groups have reported reactions giving thiazoloquinazoline compounds, probably the most interesting of which is the cyclization-ring expansion of the aziridine thiourea derivative **225** to the dihydrothiazolo[2,3-*b*]quinazoline **226** in hydrochloric acid of Howard and Klein.³⁹⁵ Other preparations of this ring system involve the treatment of 1-(2-carbethoxyphenyl)-2-thioureas with α -chloro³⁹⁶⁻³⁹⁸ or α -bromo^{396,397} ketones or with vicinal dibromides.³⁹⁸ Tetrahydro salt

³⁸⁷ E. G. Howard and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.* **82**, 158 (1960).

³⁸⁸ S. M. Khripak, A. A. Dobosh, and I. V. Smolanka, *Khim. Geterotsikl. Soedin.*, 567 (1973).

³⁸⁹ J. Schoen and S. Fladro, *Rocz. Chem.* **39**, 479 (1965).

³⁹⁰ S. Demerac, L. K. Dalton, and B. C. Elmes, *Aust. J. Chem.* **25**, 2651 (1972).

³⁹¹ H. Schulte, *Chem. Ber.* **87**, 820 (1954).

³⁹² F. Bergel and A. R. Todd, *J. Chem. Soc.*, 26 (1938).

³⁹³ A. A. Watson, S. C. Nesnow, and G. B. Brown, *J. Org. Chem.* **38**, 3046 (1973).

³⁹⁴ T. B. Johnson and N. A. Shepard, *Amer. Chem. J.* **46**, 345 (1911).

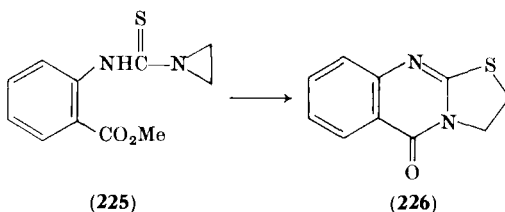
³⁹⁵ J. C. Howard and G. Klein, *J. Org. Chem.* **27**, 3701 (1962).

³⁹⁶ M. S. Dhatt and K. S. Narang, *J. Org. Chem.* **20**, 302 (1955).

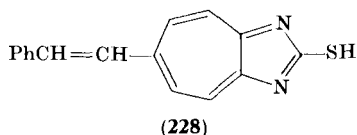
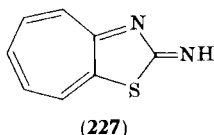
³⁹⁷ M. S. Dhatt and K. S. Narang, *Res. Bull. East Punjab Univ.* **36**, 139 (1953); *Chem. Abstr.* **49**, 4660c (1955).

³⁹⁸ M. C. Khosla, O. P. Vig, I. S. Gupta, and K. S. Narang, *J. Sci. Ind. Res.* **12B**, 466 (1953); *Chem. Abstr.* **49**, 1059 (1955).

derivatives of this type may be prepared by treatment of 1-alkyl-3-(cyclohexanon-2-ylmethyl)-2-thioureas with α -haloacetones.³⁹⁹



Interesting highly colored compounds were reported to be prepared by treatment of 2-substituted tropones with thiourea. Thus the orange or yellow 3-aza-1-thiaazulenes **227**^{400,401} are formed from 2-chlorotropones; however, the scarlet diazaazulene **228**⁴⁰² was produced from a 2-methoxytropone under the influence of sodium ethoxide.



Reactions leading to two fused five-membered rings may be performed using thiourea-type reactants. Thus cyclization of 1-(*N*-carbethoxythiocarbamoyl)pyrrole (**229**) in hot quinoline gives 1,2-dihydropyrrolo-[1,2-*c*]imidazolin-7-one-2-thione⁴⁰³ (**230**); compounds of this type may also be prepared from 1-(*N*-phenylthiocarbamoyl)pyrrole by treatment with thiophosgene.⁴⁰⁴ A completely saturated analog of **230** has been reported as having been prepared from a thiourea by Stanovnik and Tišler.⁴⁰⁵ Fused five-membered rings, the cyclopenta[*d*]imidazolines⁴⁰⁶

³⁹⁹ G. Jaenecke and H. J. Mallon, *Z. Chem.* **8**, 463 (1968).

⁴⁰⁰ I. Murata and T. Tezuka, *Tohoku Daigaku Hi-sui Yoeki Kagaku Kenkyusho Hokoku* **10**, 257 (1961); *Chem. Abstr.* **56**, 3483 (1962).

⁴⁰¹ T. Nozoe, S. Ito, K. Kitahara, and T. Ozeki, *Tohoku Daigaku Hi-sui Yoeki Kagaku Kenkyusho Hokoku* **10**, 251 (1961); *Chem. Abstr.* **55**, 25917 (1961).

⁴⁰² H. Matsumuta, *J. Chem. Soc. Japan (Nippon Kagaku Zasshi)* **78**, 669 (1957).

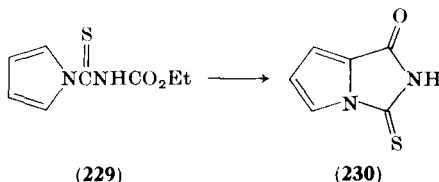
⁴⁰³ E. P. Papadopoulos, *J. Org. Chem.* **38**, 667 (1973).

⁴⁰⁴ E. P. Papadopoulos, *J. Org. Chem.* **31**, 3060 (1966).

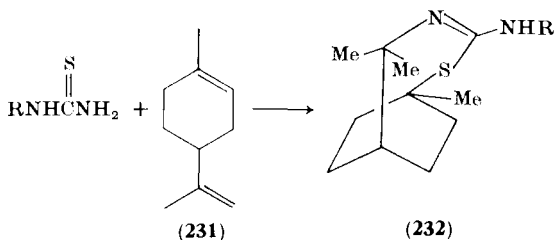
⁴⁰⁵ B. Stanovnik and M. Tišler, *Croat. Chem. Acta* **35**, 167 (1963); *Chem. Abstr.* **60**, 6840 (1964).

⁴⁰⁶ I. V. Smolanka, T. A. Krasnitskaya, and E. G. Mel'nik, *Ukr. Khim. Zh.* **38**, 793 (1972); *Chem. Abstr.* **77**, 152039 (1972).

and the cyclopenta[*d*]thiazolines,⁴⁰⁷ have been reported by Smolanka and co-workers.



The reaction of thioureas with terpenes has been employed to prepare an interesting series, the thiazabicyclo[4.2.2]dec-3-enes (**232**). The



reaction, illustrated with limonene (**231**), has been studied with thiourea itself in the cases of none different starting terpenes all leading to **232** (R = H) in yields of 26–44%.⁴⁰⁸ The reaction also leads to *N*-substituted derivatives of **232** (R = Me, Ph) with monosubstituted thioureas.⁴⁰⁹ Another heterocyclic compound prepared from thiourea and a terpene starting material is the expected tricyclic pyrimidine derived from 3-carbethoxycamphor.⁴¹⁰

Other ring types prepared from thioureas include those of Petersen and Heitzer, who prepared the naphthoxathiolones **233** (X = O, Y = OH)⁴¹¹ from 2-(2-methylpropanal-2-yl)-1,4-naphthoquinone and **233** (X = NH, Y = H)⁴¹² starting with a tetrahydrobenz[*g*]indol-5-one, each through reaction with thiourea in hydrochloric acid. Kaushal and Narang⁴¹³ prepared a series of dihydrothiazolo[4,5-*c*]cinnolines

⁴⁰⁷ I. V. Smolanka and N. K. Man'ko, *Ukr. Khim. Zh.* **36**, 589 (1970); *Chem. Abstr.* **73**, 98856 (1970).

⁴⁰⁸ L. C. King, L. A. Subluskey, and E. W. Stern, *J. Org. Chem.* **21**, 1232 (1956).

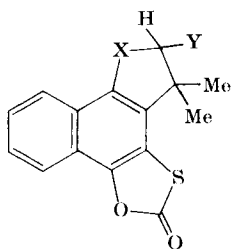
⁴⁰⁹ L. C. King and E. W. Stern, *J. Org. Chem.* **23**, 1928 (1958).

⁴¹⁰ M. Polonovski and D. Libermann, *Bull. Soc. Chim. Fr.*, 1073 (1947).

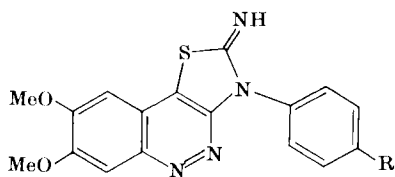
⁴¹¹ S. Petersen and H. Heitzer, *Justus Liebigs Ann. Chem.* **764**, 28 (1972).

⁴¹² S. Petersen and H. Heitzer, *Justus Liebigs Ann. Chem.* **764**, 50 (1972).

⁴¹³ A. N. Kaushal and K. S. Narang, *Indian J. Chem.* **10**, 675 (1972); *Chem. Abstr.* **78**, 4202a (1973).

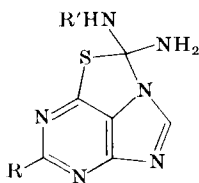


(233)



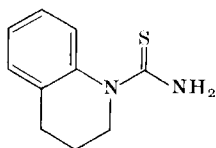
(234)

(234) from 3-bromo-4-chlorocinnolines and monosubstituted thioureas. Another unusual heterotricyclic system formed from thioureas is the thiazolo[3,4,5-*g,h*]purine **235**, which results in low yield on treatment of 6-chloropurines with thioureas.⁴¹⁴

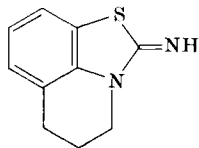


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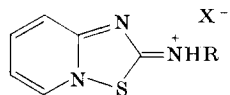
Two modifications of the well-known benzothiazole preparation have been employed to prepare unusual heteropolycycles. König *et al.*⁴¹⁵ treated 1-thiocarbamoyl-1,2,3,4-tetrahydroquinoline (**236**) with bromine in chloroform to give the thiazolo[3,4,5-*j,i*]quinoline derivative **237**. In a process which requires disruption of the resonance stabilization of the pyridine ring, Harris⁴¹⁶ reported that treatment of 1-(2-pyridyl)-2-thioureas with sulfonyl chloride or with bromine gives the hydrohalide salts of 2-imino-2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridines (**238**).



(236)



(237)



(238)

⁴¹⁴ C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.* **31**, 1417 (1966).

⁴¹⁵ W. König, W. Kleist, and J. Götze, *Ber.* **64**, 1664 (1931).

⁴¹⁶ R. L. N. Harris, *Aust. J. Chem.* **25**, 993 (1972).

Advances in the Chemistry of Chrom-3-enes

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Milano, Italy*

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I. Introduction

The aim of this review is to survey the advances in the chemistry of chrom-3-enes (2*H*-1-benzopyrans, chrom- Δ^3 -enes, α -chromenes)¹ in the last decade. This subject was previously summarized by Wawzonek² in 1951. A brief but clear treatment of chrom-3-ene chemistry can be found in Dean's book³ (1963), where a detailed account is given of all the natural products known at that time. A section of a recent book on the synthesis of natural compounds has been dedicated to chromenes.⁴

The present review will not deal with chrom-2-enes, nor with benzo-pyrylium salts, nor with ring-fused pyrano-heterocycles. The reader

¹ Although the name 2*H*-1-benzopyran is preferred by *Chemical Abstracts*, the more common nomenclature chrom-3-ene will be used throughout this review.

² S. Wawzonek, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 2, p. 277. Wiley, New York, 1951.

³ F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth, London, 1963.

⁴ F. M. Dean, in "The Total Synthesis of Natural Products" (J. ApSimon, ed.), p. 467. Wiley (Interscience), New York, 1973.

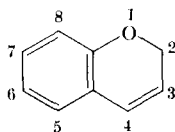
interested in the preparation and applications of the numerous photochromic spiropyrans is referred to the recent book by Bertelson.⁵ Surveys of the chemistry of hashish have also appeared.⁶

Literature has been searched through Volume 78 of *Chemical Abstracts* and through 1973 issues of the most accessible journals.

II. Physical Properties

No quantum mechanical calculation or similar theoretical treatment seems to have been dedicated to chrom-3-ene⁷ or to its simple derivatives. Interatomic distances and angles of two bromo derivatives of natural chromenes have been obtained by X-ray analysis,^{8,9} The UV absorption,¹⁰ emission,¹¹ fluorescence, and fluorescence excitation spectra¹² of some 2,2-dialkylchromenes have been studied in connection with their photochromic behaviour.

The nuclear magnetic resonance (NMR) spectrum of chrom-3-ene (**1**) has been measured¹³ and the sign of coupling constants between protons on the hetero ring obtained from a study of double quantum transitions.¹³ An inter-ring coupling ($J_{4,8}$) has been detected.¹⁴⁻¹⁶ In



(1)

⁵ R. C. Bertelson, in "Techniques of Chemistry" (A. Weissberger, ed.), Vol. III: Photochromism. Wiley, New York, 1971.

⁶ R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturstoffe* **25**, 175 (1967); Ciba Foundation Symposium on the Chemistry and Botany of Cannabis," (C. R. B. Joyce and S. H. Curry, eds.), Churchill, London, 1970; "Abstract of Symposium on the Chemistry and Biological Activity of Cannabis," Apotheker Societaten, Stockholm, 1971; R. K. Razdan, in "Progress in Organic Chemistry" (J. Cook and W. Carruthers, eds.), Vol. 8, Butterworth, London, 1973.

⁷ For the sake of brevity, the numbering of the double bond will be omitted when not necessary.

⁸ R. G. Paton, E. N. Maslen, and K. J. Watson, *Acta Crystallogr.* **22**, 120 (1967).

⁹ W. L. Parker, J. S. Flynn, and F. P. Baer, *J. Amer. Chem. Soc.* **90**, 4723 (1968).

¹⁰ N. V. Tyler and R. S. Becker, *J. Amer. Chem. Soc.* **92**, 1289 (1970).

¹¹ N. V. Tyler and R. S. Becker, *J. Amer. Chem. Soc.* **92**, 1295 (1970).

¹² R. S. Becker, E. Dolan and D. E. Balke, *J. Chem. Phys.* **50**, 239 (1969).

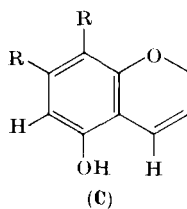
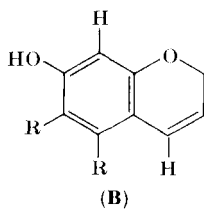
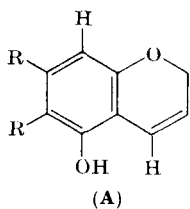
¹³ L. Lunazzi and F. Taddei, *J. Mol. Spectrosc.* **25**, 113 (1968).

¹⁴ J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

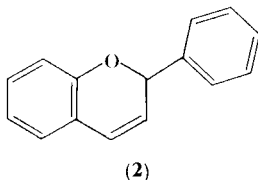
¹⁵ A. Arnone, G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron Lett.*, 4201 (1967).

¹⁶ E. V. Lassak and J. T. Pinhey, *J. Chem. Soc. C*, 2000 (1967).

5-hydroxychromenes H_4 is deshielded with respect to the parent compound, whereas acetylation of the OH group induces a marked diamagnetic shift ($\Delta\delta = 0.3\text{--}0.4$).¹⁵ These effects, of steric origin,¹⁵ together with the 4,8 interaction, have been used by many authors to distinguish between differently annellated pyran rings in polycyclic



natural products, as illustrated by the examples **A,B,C** (**A**: acetyl shift and $J_{4,8}$; **B**: no acetyl shift but $J_{4,8}$; **C**: acetyl shift, no $J_{4,8}$). When the *peri* group is a methoxyl, or an *N*-methyl, the nuclear Overhauser effect (NOE) reveals the interaction with H_4 .¹⁷⁻¹⁹ In some flav-3-enes (2-phenylchrom-3-enes, **2**) the ABX pattern of the 2,3,4 protons has been analyzed, and signs of the coupling constants were measured.²⁰ The magnitude (-2 Hz) of $J_{2,4}$ indicates a 90° angle between H_2 and H_4 , and supports the equatorial orientation of the phenyl group. The



absence of this allylic coupling in 3-acetoxyflavenes⁷ has been invoked to suggest that the phenyl is axial.²¹ Solvent shift effects helped in the assignment of the substituents on the aromatic ring of natural chromenes.^{22,23}

¹⁷ T. Tominatsu, M. Hashimoto, T. Shingu, and K. Tori, *Tetrahedron* **28**, 2003 (1972).

¹⁸ J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.* **23**, 1881 (1970).

¹⁹ H. D. Locksley, A. J. Quillinan, and F. Scheinmann, *J. Chem. Soc. C*, 3804 (1971).

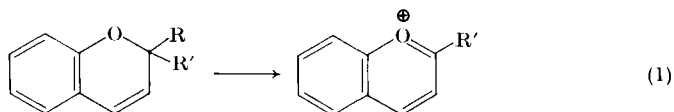
²⁰ J. W. Clark-Lewis, *Aust. J. Chem.* **21**, 2059 (1968).

²¹ H. Aft, R. R. Grant, and R. J. Molyneux, *Tetrahedron* **23**, 1963 (1967).

²² H. W. Moore and K. Folkers, *J. Amer. Chem. Soc.* **88**, 564 (1966).

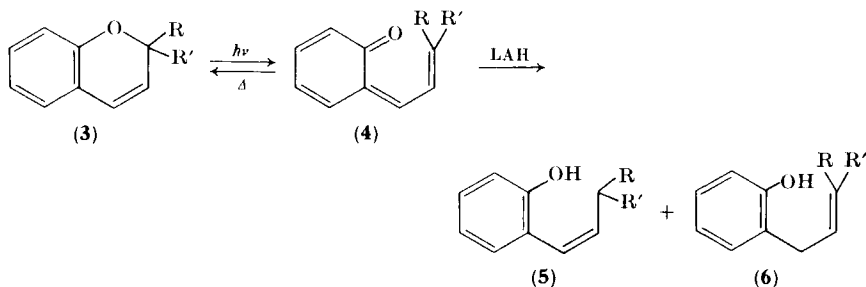
²³ T. Anthonsen, *Acta Chem. Scand.* **22**, 352 (1968).

Mass spectra of chromene,²⁴ 2-alkylchromenes,²⁴⁻²⁸ and flavenes²⁹ have been studied. The fragmentation is dominated by the loss of one



of the substituents on C-2, to give a stable benzopyrylium ion, which does not break down readily [Eq. (1)]. When R is H, and R' is aryl or alkyl, hydrogen is lost preferentially. In the case of 6-hydroxy derivatives, quinonoid forms can be written for these ions.^{24,26}

Much interest has been devoted to the photochromic behaviour of simple chromenes, especially because of practical applications of spiropyrans, particularly indolinospirans.⁵ Kolc and Becker³⁰ have been able to demonstrate the *o*-quinoneallide structure of the colored form **4**, by producing it in THF at -75° and trapping by reduction with LiAlH_4 . It is concluded^{31,32} that the same intermediates occur when spiropyrans are irradiated, because only the pyran moiety has an



active role in the photochromism. Molecular orbital-self-consistent field (MO-SCF) calculations³³ on the open form **4** suggest that the bonds are benzenoid-like, but no definite results were obtained on the differences between the *cis* and the *trans* forms.

²⁴ B. Willhalm, A. F. Thomas, and F. Gautschi, *Tetrahedron* **20**, 1185 (1964).

²⁵ C. S. Barnes and J. L. Occolowitz, *Aust. J. Chem.* **17**, 975 (1964).

²⁶ H. Morimoto, T. Shima, I. Imada, M. Sasaki, and A. Ouchida, *Justus Liebigs Ann. Chem.* **702**, 137 (1967).

²⁷ A. M. Duffield, *Org. Mass. Spectrom.* **2**, 965 (1969).

²⁸ W. J. Richter, J. G. Liehr, and P. Schulze, *Tetrahedron Lett.*, 4503 (1972).

²⁹ A. Pelter and P. Stainton, *J. Chem. Soc. C*, 1933 (1967).

³⁰ J. Kolc and R. S. Becker, *J. Phys. Chem.* **71**, 4045 (1967).

³¹ J. Kolc and R. S. Becker, *Photochem. Photobiol.* **12**, 383 (1970).

³² C. Balny, M. Hannezo, and A. Hinnen, *J. Chim. Phys.* **64**, 1815 (1967).

³³ L. Edwards, J. Kolc, and R. S. Becker, *Photochem. Photobiol.* **13**, 423 (1971).

Data on the molecular refraction and Raman absorption of chrom-3-ene have been reported.³⁴

III. Natural Substances

Almost every class of natural phenolic compounds contains examples of substances with a 2,2-dialkylchromene ring, and the number of those that are discovered increases every year. It would be difficult to give an exhaustive list of these compounds. Their chemistry will be discussed here only when it is related to some particular behavior of the benzopyran ring. Examples include simple chromenes substituted in the aromatic ring,^{3,4,35-44} benzodipyrans,^{3,39} dimers of chromenes,⁴⁵ naphthopyrans,^{46,47} quinones,⁴⁸ flavones,⁴⁹ flavonols,⁴⁹ chalcones,⁴⁹ flavanones,⁴⁹ isoflavonoids,⁵⁰ rotenoids,⁵⁰ pterocarpanes,⁵⁰ coumarins,^{17,51-53} 3-aryl-4-hydroxycoumarins,⁵⁰ 4-phenylcoumarins,⁵⁴ chroma-

³⁴ P. Maitte, *Ann. Chim. (Paris)* **10**, 431 (1955).

³⁵ F. Bohlmann and M. Grenz, *Ber.* **103**, 90 (1970).

³⁶ N. A. Sørensen, *Abstr. Intern. Symp. Natural Products, 3rd. Melbourne, 1960*, p. 43.

³⁷ L. F. Bjeldanes and T. A. Geissman, *Phytochemistry* **8**, 1293 (1969).

³⁸ T. Anthonsen, *Acta Chem. Scand.* **23**, 3605 (1969).

³⁹ K. Shima, S. Hisada, I. Inagaki, *Yakugaku Zasshi* **91**, 1124 (1971); *Chem. Abstr.* **76**, 14258.

⁴⁰ D. R. Taylor and J. A. Wright, *Phytochemistry* **10**, 1665 (1971).

⁴¹ W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.* **90**, 4716 (1968).

⁴² R. D. Allan, R. L. Correll, and R. J. Wells, *Tetrahedron Lett.*, 4673 (1969).

⁴³ A. M. Duffield and P. M. Jefferies, *Aust. J. Chem.* **15**, 812 (1962); **16**, 123 (1963).

⁴⁴ K. Makino, A. Yagi, and I. Nishioka, *Chem. Pharm. Bull.* **21**, 149 (1973).

⁴⁵ T. R. Kasturi and Mani Thomas, *Tetrahedron Lett.*, 2573 (1967); T. R. Kasturi, Mani Thomas, and E. M. Abraham, *Indian J. Chem.* **11**, 91 (1973).

⁴⁶ W. Sandermann and M. H. Simatupang, *Ber.* **97**, 588 (1964).

⁴⁷ A. R. Burnett and R. H. Thomson, *J. Chem. Soc. C*, 854 (1968).

⁴⁸ R. H. Thomson, "Naturally Occurring Quinones," Academic Press, New York, 1971.

⁴⁹ K. Venkataraman, *Phytochemistry* **11**, 1571 (1972); L. Merlini, *ibid.* **12**, 669 (1973).

⁵⁰ E. Wong, *Fortschr. Chem. Org. Naturstoffe* **28**, 1 (1970).

⁵¹ W. B. Whalley, in "Chemistry of Heterocyclic Compounds" (R. C. Elderfield ed.), Vol. 7, p. 1. Wiley, New York, 1961.

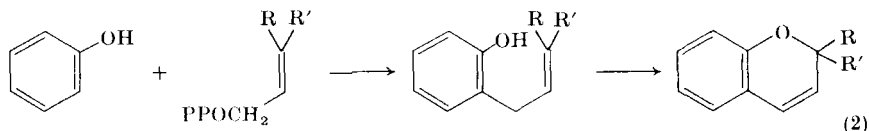
⁵² H. R. Arthur and W. D. Ollis, *J. Chem. Soc.*, 3910 (1963).

⁵³ M. Furer, T. R. Govindachari, and B. S. Joshi, *Indian J. Chem.* **8**, 198 (1970).

⁵⁴ W. R. Chan, D. R. Taylor, and C. R. Willis, *J. Chem. Soc. C*, 2541 (1967); D. E. Games and N. J. Haskins, *Chem. Commun.*, 1005 (1971) and refs. quoted therein.

nones,⁵⁵⁻⁵⁷ chromones,^{58,59} xanthenes,⁶⁰ carbazole alkaloids,⁶¹ quinoline alkaloids,⁶² acridines,⁶³ and a recent example of an indole alkaloid.⁶⁴

All natural 2,2-dialkylchromenes are believed⁶⁵ to be derived *in vivo* from alkylation of a phenol or a suitable precursor with an allyl pyrophosphate [Eq. (2)]. Surprisingly, no biosynthetic work has been



carried on chromenes, except for ubiquinomenol, which incorporates 2-¹⁴C-labeled mevalonic acid when this is injected into rats.⁶⁶ A very recent communication⁶⁷ gives the first report of the biogenesis of a chromene from an isoprenoid precursor.

Different pathways might be followed in the biosynthesis of pyrano-quinones, such as **7** and **8**,⁴⁸ and of the only natural 2-methylenechromene.⁴⁴ Various mechanisms have been postulated or suggested for the

⁵⁵ E. Guerreiro, G. Kunesch, and J. Polonsky, *Phytochemistry* **10**, 2139 (1971).

⁵⁶ G. H. Stout and K. D. Sears, *J. Org. Chem.* **33**, 4185 (1968); G. H. Stout, G. K. Hickernell, and K. D. Sears, *ibid.* **33**, 4191 (1968).

⁵⁷ I. Carpenter, E. J. McGarry, and F. Scheinmann, *J. Chem. Soc. C*, 3783 (1971).

⁵⁸ F. M. Dean and D. H. Taylor, *J. Chem. Soc.*, 113 (1966); F. M. Dean and M. L. Robinson, *Phytochemistry* **10**, 3221 (1971).

⁵⁹ D. R. Taylor and J. A. Wright, *Rev. Latinoamer. Quim.* **2**, 84 (1971).

⁶⁰ I. Carpenter, M. D. Locksley, and F. Scheinmann, *Phytochemistry* **8**, 2013 (1969).

⁶¹ S. Kapil, in "The Alkaloids" (F. Manske, ed.), Vol. 13, p. 273, Academic Press, New York, 1971.

⁶² H. T. Openshaw, in "The Alkaloids" (F. Manske, ed.), Vol. 9, p. 224, Academic Press, New York 1967.

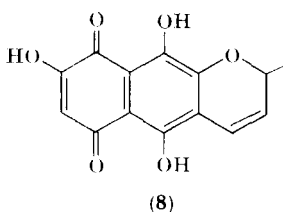
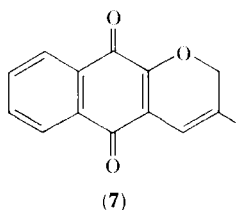
⁶³ J. Schneider, E. L. Evans, E. Grunberg, and R. I. Fryer, *J. Med. Chem.* **15**, 266 (1972) and refs. quoted therein.

⁶⁴ B. Danieli, P. Manitto, F. Ronchetti, G. Russo, and G. Ferrari, *Experientia* **28**, 250 (1972).

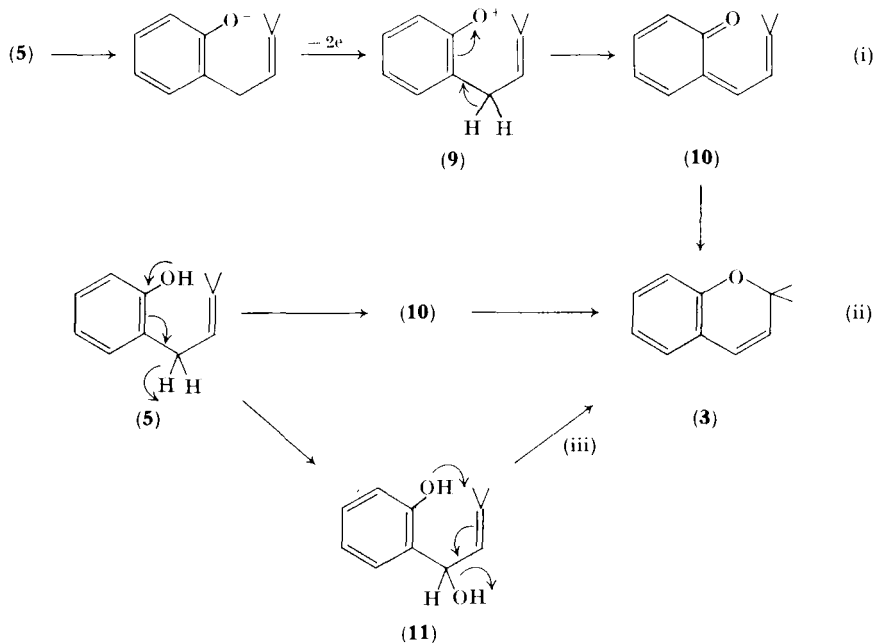
⁶⁵ W. D. Ollis and I. O. Sutherland, "Recent Developments in the Chemistry of Natural Phenolic Substances," Pergamon, Oxford, 1961; W. D. Ollis, *Experientia* **22**, 777 (1966); W. D. Ollis and O. R. Gottlieb, *Chem Commun.*, 1396 (1968).

⁶⁶ T. Ramasarma and V. C. Joshi, *Bull. Nat. Inst. Sci. India* **28**, 19 (1965) [*Chem. Abstr.* **66**, 27120 (1967)]; V. C. Joshi, J. Jayaraman, and T. Ramasarma, *Biochem. J.* **92**, 9C (1964); V. C. Joshi, J. Jayaraman, and T. Ramasarma, *Indian J. Exp. Biol.* **1**, 113 (1963) [*Chem. Abstr.* **59**, 10575 (1963)]; and *Biochem. Biophys. Res. Commun.* **12**, 247 (1963).

⁶⁷ K. T. Suzuki and S. Nozoe, *Chem. Commun.*, 1166 (1972).



ring closure step [(Eq. (2))] on the basis of similar *in vitro* reactions, although none of them is yet supported by *in vivo* experiments. These hypotheses are reported here, however, because they have been, and still can be stimulating suggestions for new synthetic work. In the first pathway that was proposed⁶⁵ (Scheme 1), an isoprenylated phenol may

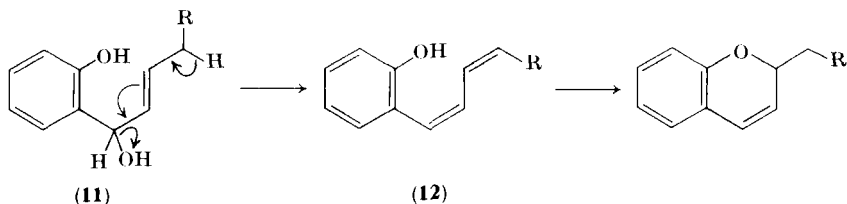


SCHEME 1

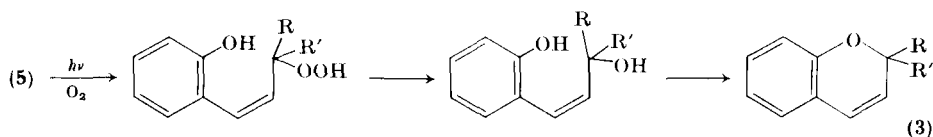
undergo a two-electron oxidation to the cation **9**, which can lose a proton to give the quinonemethide **10** (i). The ring closure to the chromene occurs by an electrocyclic reaction. A more widely accepted variation of this hypothesis⁶⁸ requires the abstraction of a hydride ion

⁶⁸ A. B. Turner, *Quart. Rev.* **18**, 347 (1964).

from the benzylic position by a quinonelike coenzyme (ii). Alternatively, oxidation of **5** at the benzylic position⁶⁹ could produce the alcohol **11**, which can give **3** by concerted elimination of water or through the

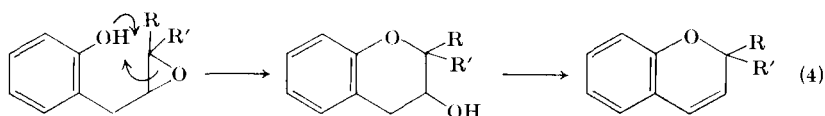


intermediate benzylic cation. It has also been suggested⁷⁰ that this alcohol could be derived by condensation of citral or an equivalent unit with a phenol. Again, the conversion of **11** into a diene (**12**) has been postulated.⁷¹ The photooxidation of the allylic side chain of **5** has been



proposed⁷² as the oxidative step in the ring closure sequence [Eq. (3)].

The epoxidation of the double bond of **5** has also been postulated,⁷³



probably by analogy with the behavior of quinoline alkaloids⁶² [Eq. (4)].

Most of the natural 2,2-dialkylchromenes are derived from a single C_5 isoprenoid chain (**3**, $R = R' = \text{Me}$). Recently, however, some polyisoprenoid chromenes have been isolated: gambogic acid (**13**),⁷⁴ flemingins (**14**),⁷⁵ cannabichromene (**15**) and cannabichromenic acid

⁶⁹ R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturstoffe* **25**, 201 (1967).

⁷⁰ L. Crombie and R. Ponsford, *Tetrahedron Lett.*, 4557 (1968).

⁷¹ V. V. Kane and R. K. Razdan, *Tetrahedron Lett.*, 591 (1969).

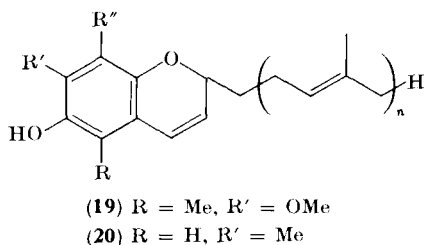
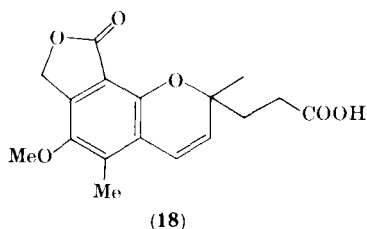
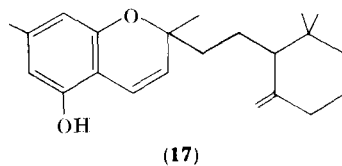
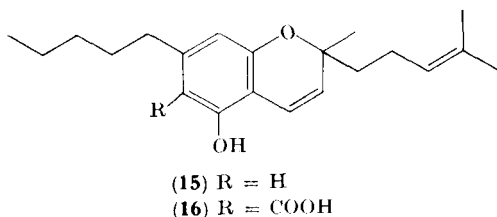
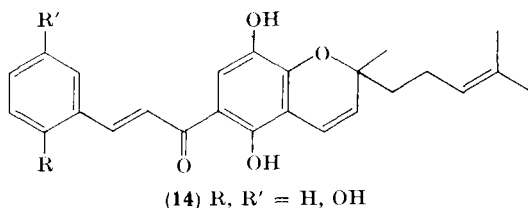
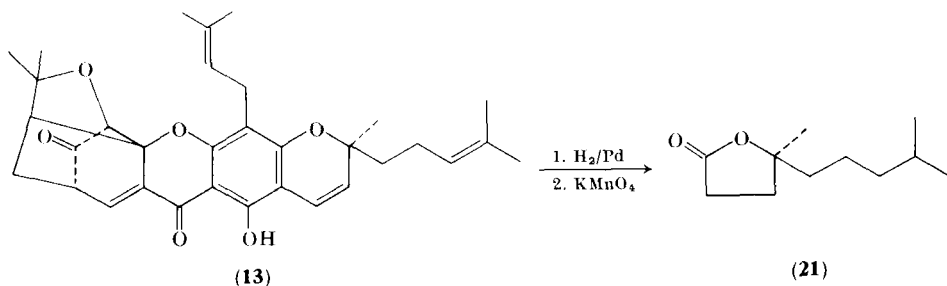
⁷² J. C. Fourrey, J. Rondest, and J. Polonsky, *Tetrahedron* **26**, 3839 (1970).

⁷³ F. Bohlmann and M. Grenz, *Ber.* **103**, 90 (1970).

⁷⁴ W. D. Ollis, M. V. J. Ramsay, I. O. Sutherland, and S. Mongkolsuk, *Tetrahedron* **21**, 1453 (1965).

⁷⁵ G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron* **24**, 497 (1968); B. Cardillo, A. Gennaro, L. Merlini, G. Nasini, and S. Servi, *Phytochemistry* **12**, 2027 (1973).

(16),⁶ and many carbazole alkaloids⁶¹ contain a C₁₀ chain, whereas the mold metabolites siccanochromene (17)⁷⁶ and mycochromenic acid (18),⁷⁷ respectively, contain or are derived⁷⁸ from a farnesyl chain.



⁷⁶ K. Hirai, K. T. Suzuki, and S. Nozoe, *Tetrahedron* **27**, 6057 (1971); S. Nozoe and K. T. Suzuki, *ibid.* **27**, 6063 (1971); S. Nozoe and K. Hirai, *ibid.* **27**, 6073 (1971).

⁷⁷ I. M. Campbell, C. M. Calzadilla, and N. J. McCorkindale, *Tetrahedron Lett.*, 5107 (1966).

⁷⁸ L. Canonica, W. Kroszczyński, B. M. Ranzi, B. Rindone, C. Scolastico, and E. Santaniello, *J. Chem. Soc. Perkin Trans. I*, 2639 (1972).

As for the 6-hydroxychromenes, such as ubiquchromenol (**19**, $n = 9$) and plastochromenol (**20**, $n = 8$), related to ubiquinones and similar long-chain quinones,⁴⁸ there has been some controversy about their being true natural products or artifacts.⁷⁹ All the quinones, with any value of n from zero to 9, have been converted into the corresponding chromenols.

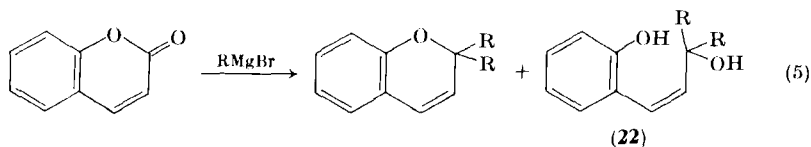
The optical activity of natural 2,2-dialkylchromenes with two different alkyl groups is difficult to assess with certainty, owing to the combined effects of difficulty of purification (usually they are oils or low-melting solids) and of the low intensity of the chromophore. The activity of ubiquchromenol and related compounds has been questioned, and it seems now certain that cannabichromene and cannabicyclol are inactive.⁶ The only unequivocal case is that of gambogic acid (**13**), which has been degraded to *R*(+)-4,8-dimethyl-4-hydroxynonanoic acid lactone (**21**) of high optical purity.⁸⁰ The point could be of relevance in connection with the biosynthesis. If the quinonemethides (**10**) are intermediates, their cyclization to chromenes could occur without enzymic control, and thus give rise to optically inactive compounds.

IV. Syntheses

Much progress has been made in the last ten years in the synthesis of chrom-3-enes. Most of the activity has been stimulated by the discovery of new natural products and by the suggestions of possible biosynthetic pathways (see Section III). For results prior to 1963, the reader should consult Dean's book³ and Wawzonek's review.²

A. FROM A PREFORMED HETERO RING

The reaction of coumarins with a Grignard reagent to give 2,2-dialkylchromenes [Eq. (5)] has been known for a long time.^{2,3} This synthesis has continued to be used, without modification, owing to the

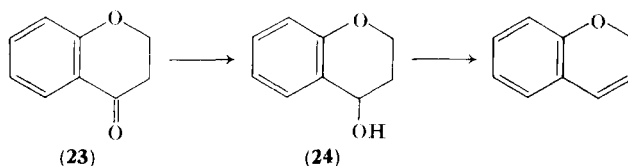


⁷⁹ R. A. Morton, "The Biochemistry of Quinones," Academic Press, New York, 1965.

⁸⁰ G. Cardillo and L. Merlini, *Tetrahedron Lett.*, 2529 (1967).

accessibility of many coumarins.^{6,81-86} With excess of the reagent and more forcing conditions, the ring can open to give 2-(2-alkyl-2-hydroxy-) but-3-enylphenols (**22**),^{82,86} from which the chromene can be recovered by acid treatment.⁸⁷⁻⁸⁹ The same reaction has been applied to prepare 2,2-diphenyl derivatives,^{90,91} and occasionally it has given 2,4-diphenylchromenes.⁸⁵

Chromenes are easily obtained by dehydration of 4-chromanols (**24**), in their turn readily available by reduction of 4-chromanones (**23**). The parent compound chrom-3-ene has been prepared by this method⁹² in 75-80% yield, via Meerwein-Ponndorf reduction and dehydration by azeotropic distillation over CuSO_4 . Other reducing agents are metal



hydrides,^{93,94} and dehydration can be performed either with *p*-toluene-sulfonic acid,^{92,94} acetic acid,^{55,95} and acetyl chloride,⁹⁶ or by heating with Al_2O_3 ⁹³ or KHSO_4 ^{97,98} or by pyrolysis of the alcohol itself⁹⁶ or of the acetate.⁹⁹ A similar sequence can be carried out starting from 3-chromanones,^{100,101} but these are usually less accessible materials than

⁸¹ H. Fukami, M. Nakayama, and M. Nakajima, *Agr. Biol. Chem.* **25**, 243 (1961).

⁸² R. K. Razdan, W. R. Thompson, H. G. Pars, and F. E. Granchelli, *Tetrahedron Lett.*, 3405 (1967).

⁸³ C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.* **30**, 4114 (1965).

⁸⁴ C. E. Cook and M. E. Wall, *J. Org. Chem.* **33**, 2998 (1968).

⁸⁵ J. Cottam and R. Livingstone, *J. Chem. Soc.*, 5228 (1964).

⁸⁶ J. Cottam and R. Livingstone, *J. Chem. Soc.*, 6646 (1965).

⁸⁷ S. Ray, P. K. Grover, and N. Anand, *Indian J. Chem.* **8**, 961 (1970).

⁸⁸ C. E. Cook and C. E. Twine, *Chem. Commun.*, 791 (1968).

⁸⁹ G. Cardillo, R. Cricchio, L. Merlini, and G. Nasini, *Gazz. Chim. Ital.* **99**, 612 (1969).

⁹⁰ W. D. Cotterill and R. Livingstone, *J. Chem. Soc. C*, 1758 (1970).

⁹¹ G. A. Holmberg and F. Malmström, *Acta Chem. Scand.* **22**, 995 (1968).

⁹² F. Baranton, G. Fontaine, and P. Maitte, *Bull. Soc. Chim. Fr.*, 4203 (1968).

⁹³ R. Huls, *Bull. Soc. Chim. Belges* **66**, 409 (1957); **67**, 22 (1958); **68**, 325 (1959).

⁹⁴ M. L. Wolfrom, E. W. Koos, and H. B. Bhat, *J. Org. Chem.* **32**, 1058 (1967).

⁹⁵ R. Livingstone, *J. Chem. Soc.*, 76 (1962).

⁹⁶ N. I. Bruckner and N. L. Bauld, *J. Org. Chem.* **37**, 2359 (1972).

⁹⁷ G. Canalini, J. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)* **57**, 1045 (1967).

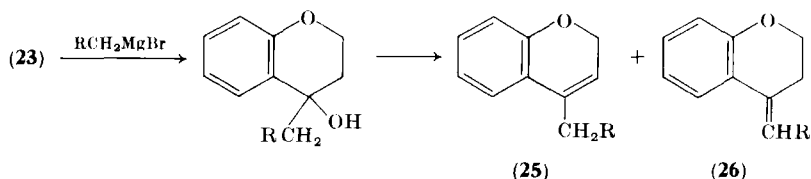
⁹⁸ D. Mowat and R. D. H. Murray, *Tetrahedron* **29**, 2943 (1973).

⁹⁹ W. E. Parham and L. D. Huestis, *J. Amer. Chem. Soc.* **84**, 813 (1962).

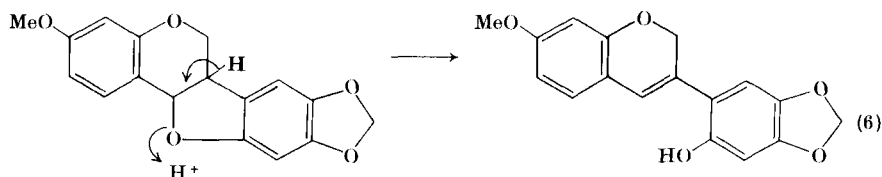
¹⁰⁰ M. Miyano and M. Matsui, *Bull. Chem. Soc. Jap.* **31**, 267 (1958).

¹⁰¹ P. K. Grover and N. Anand, *Indian J. Chem.* **7**, 196 (1969).

the 4-isomers. If Grignard reagents react with **23**, the process leads to 4-substituted chromenes (**25**).^{92,102,103} When the alkyl group in the Grignard reagent is greater than methyl, a mixture of **25** and of a 4-alkylidenechromane (**26**) is obtained.⁹² Flavenes could not be obtained



by this reaction, owing to their high sensitivity to acids and ready oxidation to pyrylium salts. On the other hand, this seems one of the preferred ways to prepare isoflav-3-enes.¹⁰⁴⁻¹⁰⁷ A similar reaction occurs in the acid-induced cleavage of the pisatin five-membered ring to give



pterocarpin [Eq. (6)]¹⁰⁸ and in the conversion of 4-aminoisoflavans into isoflavenes by treatment with HNO_2 .¹⁰⁹

The elimination of water (or acetic acid) also occurs during reductive acetylation of flavonols, leading to 3-acetoxyflav-3-enes (**27**), which are converted into flavylium salts (**28**) in the acid medium. This reaction has been the subject of much study because of the complexity of the

¹⁰² J. Colonge and A. Guyot, *Bull. Soc. Chim. Fr.*, 325 (1958).

¹⁰³ K. Weinges, W. Kaltenhäuser, M. D. Marz, E. Nader, F. Nader, J. Perner, and D. Seiler, *Justus Liebigs Ann. Chem.* **711**, 184 (1968).

¹⁰⁴ L. R. Row, A. S. R. Anjaneyulu, and C. Sri Krishna, *Curr. Sci.* **32**, 67 (1963); *Tetrahedron* **21**, 2677 (1965).

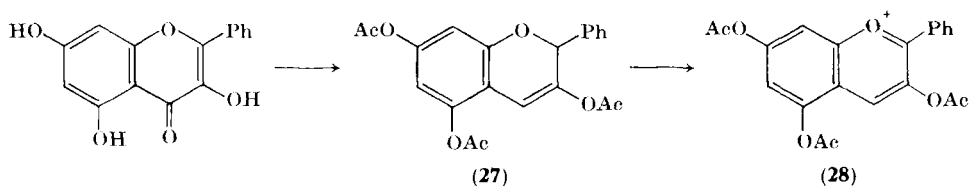
¹⁰⁵ N. Inoue, *Bull. Chem. Soc. Jap.* **37**, 606 (1964).

¹⁰⁶ C. A. Anirudhan, W. B. Whalley, and M. M. E. Badran, *J. Chem. Soc. C*, 629 (1966).

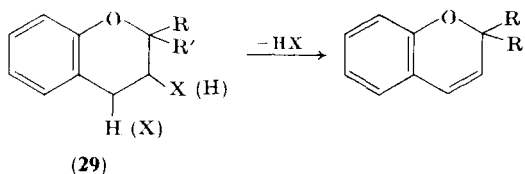
¹⁰⁷ K. H. Dudley, R. C. Corley, H. W. Miller, and M. E. Wall, *J. Org. Chem.* **32**, 2312, 2317 (1967).

¹⁰⁸ C. W. L. Bevan, A. J. Birch, B. Moore, and S. K. Mukerjee, *J. Chem. Soc.*, 5991 (1964).

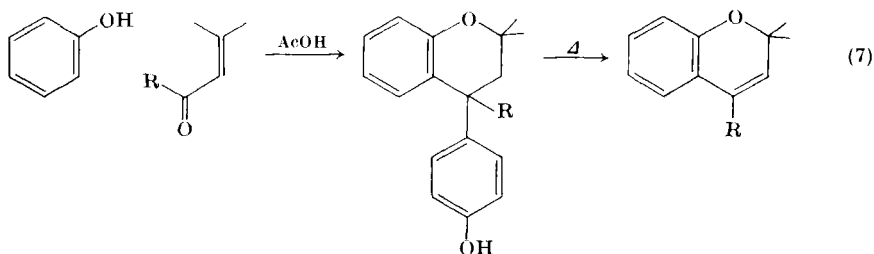
¹⁰⁹ S. Yamaguchi, S. Ito, I. Suzuki, and N. Inoue, *Bull. Chem. Soc. Jap.* **41**, 2073 (1968).



products.¹¹⁰ LiAlH_4 reduction of 3-methoxyflavones gives a mixture of 3-methoxyflav-3-enes and of 3-methoxyflav-2-enes. Acetic acid treatment converts the 2-isomer into the 3-isomer.¹¹¹ Elimination of HX ($\text{X} = \text{halogen}$) from 3- or 4-halochromanes (29) by action of bases has been used in the preparation of chromene¹¹² and flav-3-ene,^{113,114} of leucocyanidin acetate,¹¹⁵ and of 4-halochromenes.¹¹⁶ The elimination



of HBr from 3,4-dibromochromanes seems rather sensitive to the reaction conditions: 4-bromo-,¹¹⁶ a mixture of 3- and 4-bromo,¹¹⁶ and 3-bromochromenes^{9,37,95} have been obtained in different instances. 3-Bromochromenes can be prepared by dehydration of 3-bromo-4-hydroxychromanes.¹¹⁶ Similar eliminations occur in the pyrolysis of 4-ethoxychromane, of 3-alkylammoniochromanes,¹¹⁷ of chromanes



¹¹⁰ See Tominatsu¹⁷ and literature quoted therein.

¹¹¹ A. C. Waiss and L. C. Jurd, *Chem. Ind. (London)*, 743 (1968).

¹¹² H. Normant and A. Gabert, *C.R. Acad. Sci.* **235**, 1047 (1952).

¹¹³ K. G. Marathe, E. M. Philbin, and T. J. Wheeler, *Chem. Ind. (London)*, 1793 (1962).

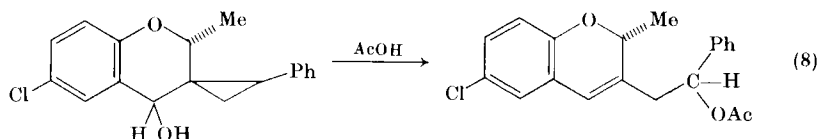
¹¹⁴ G. Descotes and D. Missos, *Synthesis*, 149 (1971).

¹¹⁵ A. K. Ganguly and T. R. Seshadri, *Curr. Sci.* **29**, 53 (1960); *Chem. Abstr.* **54**, 22605 (1960).

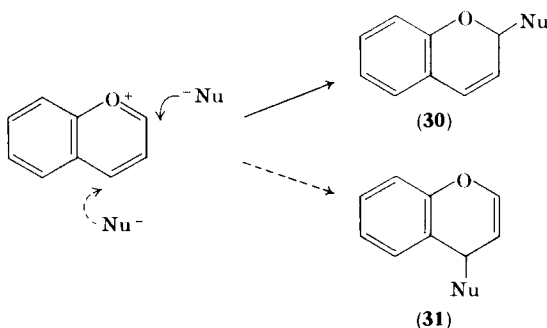
¹¹⁶ H. Hofmann and G. Salbeck, *Ber.* **104**, 168 (1971).

¹¹⁷ R. R. Wittekind, T. Capiris, and S. Lazarus, *J. Heterocycl. Chem.* **9**, 1441 (1972).

4-substituted with an ortho or para hydroxyphenyl group [Eq. (7)]^{118,119} and in the homoallylic rearrangement of 3-spirocyclopropyl-4-hydroxychromanes [Eq. (8)].¹²⁰



Nucleophilic addition to benzopyrylium salts is another route to chromenes, but the attack may occur at the positions 2 or 4, thus giving rise to chrom-3-enes (**30**) or chrom-2-enes (**31**). Thus NaBH₄ reduces simple flavylium salts to flav-2-ene¹²¹ (which, in its turn, behaves as a nucleophile and gives rise to dimeric products¹¹⁰) whereas 3-substituted



salts undergo preferential addition at the 2 position.^{122,123} Naphthopyrylium salts give both isomers.¹²⁴ 4-Chlorobenzopyrylium chloride has been shown by NMR to be in equilibrium with 2,4-dichlorochrom-3-ene in SO₂ solution.¹²⁵ Phenols attack this ion at position 2.¹²⁵ 2-Aminochromenes (and the 4-amino analogs) have been prepared

¹¹⁸ W. Baker, A. J. Floyd, J. F. W. McOmic, G. Pope, A. S. Wearing, and J. H. Wild, *J. Chem. Soc.*, 2010 (1966).

¹¹⁹ S. P. Starkov, L. V. Glushkova, *Khim. Geterotsikl. Soedin.*, 16 (1968) [*Chem. Abstr.* **69**, 77054 (1968)]; G. G. Kondrat'eva and M. N. Volkotrub, *Sin. Issled. Eff. Khim. Dobavok, Polim. Mat.*, 373 (1969) [*Chem. Abstr.* **76**, 59369 (1972)].

¹²⁰ P. Bennett, J. A. Donnelly, D. C. Meaney, and P. O'Boyle, *J. Chem. Soc. Perkin Trans. I*, 688 (1973).

¹²¹ G. A. Reynolds and J. A. Van Allan, *J. Org. Chem.* **32**, 3616 (1967).

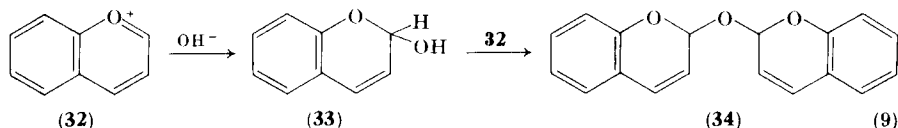
¹²² J. W. Clark-Lewis and M. I. Baig, *Aust. J. Chem.* **24**, 2581 (1971).

¹²³ K. Weinges, R. Wild, and W. Kaltenhäuser, *Z. Lebensm. Unters. Forsch.* **140**, 129 (1969); *Chem. Abstr.* **71**, 79931 (1969).

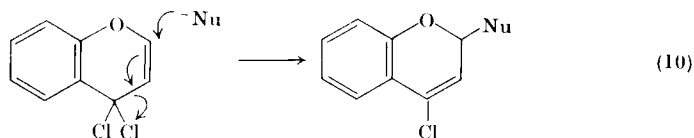
¹²⁴ Z. Muljani and B. D. Tilak, *Indian J. Chem.* **7**, 28 (1969).

¹²⁵ B. Föhlisch and D. Krockenberger, *Ber.* **101**, 3990 (1968).

starting from benzopyrylium salts and secondary amines.^{126,127} Alkaline hydrolysis of benzopyrylium perchlorate (**32**) gives 2-hydroxychromene (**33**), which adds another molecule of the salt to give the 2,2-dichromenyl



ether (**34**).¹²⁸ With 2-methylbenzopyrylium salts, dehydration is the preferred course, giving 2-methylenechromene.¹²⁹ A conversion of a 2-chromene into a 3-chromene occurs by nucleophilic attack on 4,4-dihalochrom-2-enes to give 2-substituted 4-halochrom-3-enes [Eq. (10)].¹³⁰ Normal attack at 4 can also occur.



Another pathway that has attracted much attention is the dehydrogenation of chromanes. Bromination with *N*-bromosuccinimide followed by base treatment gives fair yields,^{19,81,131-137} but the reaction may be complicated by the formation, sometimes exclusive,^{135,136,137} of a 3- or

¹²⁶ H. Hensel, *Justus Liebigs Ann. Chem.* **611**, 97 (1958).

¹²⁷ R. Sutton, *J. Org. Chem.* **37**, 1069 (1972).

¹²⁸ J. Degani, R. Fochi, and G. Spunta, *Boll. Sci. Fac. Chim. Ind. Univ. Bologna* **23**, 151 (1965); *Chem. Abstr.* **63**, 13198 (1965).

¹²⁹ M. Miyano, S. Muraki, T. Kusunoki, T. Morita, and M. Matsui, *Nippon Nogeikagaku Kaishi* **34**, 683 (1960); *Chem. Abstr.* **59**, 13929 (1963).

¹³⁰ V. A. Zagorevskii, I. D. Tsvetkova, and E. K. Orlova, *Zh. Obshch. Khim.* **34**, 1685 (1964); *Khim. Geterotsikl. Soedin.*, 786, 791 (1967); 422 (1969); E. K. Orlova, L. D. Tsvetkova, V. S. Troitskaya, V. G. Vinokurov, and V. A. Zagorevskii, *ibid.*, 429 (1969).

¹³¹ H. Fukami, J. Oda, G. Sakata, and M. Nakajima, *Agr. Biol. Chem.* **25**, 252 (1961).

¹³² A. Jefferson and F. Scheinmann, *J. Chem. Soc. C*, 175 (1966).

¹³³ F. Hoffman-La Roche, Belgian Patent 635,999 (1964); *Chem. Abstr.* **61**, 13285 (1964).

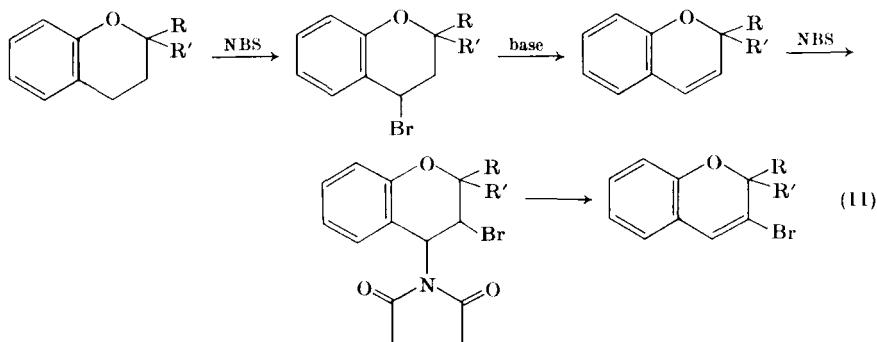
¹³⁴ C. Mercier, *Ann. Chim. (Paris)* **5**, 373 (1970); *Compt. Rend. Acad. Sci., C* **270**, 1422 (1970).

¹³⁵ F. Piozzi, P. Venturella, and A. Bellino, *Gazz. Chim. Ital.* **99**, 711 (1969).

¹³⁶ M. F. Grundon and K. J. James, *Chem. Commun.*, 1427 (1970).

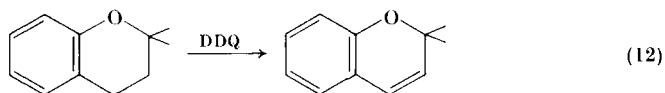
¹³⁷ A. C. Jain, V. K. Khanna, and T. R. Seshadri, *Tetrahedron* **25**, 2787 (1969).

4-bromochromene [Eq. (11)]. NMR evidence for a 3-bromochromene structure has been presented and a reasonable mechanism formulated.¹³⁶



Earlier 4-bromo structural assignments should now be reversed. The 3-bromo derivative can be transformed into the desired chromene by zinc and acid.^{19,137}

A more direct way to attain the dehydrogenation is to allow a chromane to react with a high-potential quinone, such as chloranil or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ¹³⁸) [Eq. (12)]. The reaction, usually carried on in benzene or dioxan, with yields in the



range of 40%, was first used by a Swiss group,¹³⁹ who dehydrogenated a dimer of tocopherol. Their report, however, was apparently overlooked by all the following authors, who applied the reaction in the synthesis of a variety of chromenes.^{135,140-146} In some cases the reaction

¹³⁸ D. Walker and J. D. Hiebert, *Chem. Rev.* **67**, 153 (1967).

¹³⁹ P. Schudel, H. Meyer, J. Metzger, R. Rüegg, and O. Isler, *Helv. Chim. Acta* **46**, 636 (1963).

¹⁴⁰ G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron* **24**, 4825 (1968).

¹⁴¹ A. R. Burnett and R. H. Thomson, *J. Chem. Soc. C*, 1261 (1967).

¹⁴² J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Franc, B. Rockey, and A. Pohland, *J. Amer. Chem. Soc.* **90**, 4706 (1968).

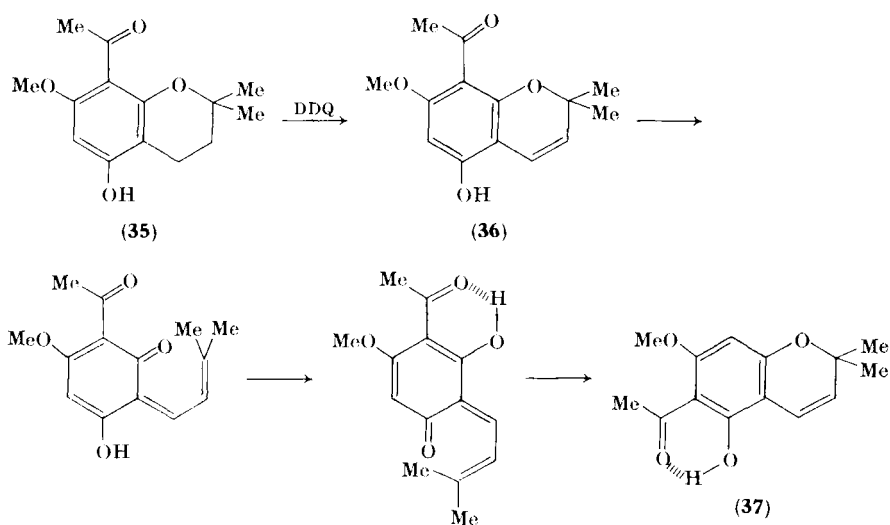
¹⁴³ R. Mechoulam, B. Yagnitinsky, and Y. Gaoni, *J. Amer. Chem. Soc.* **90**, 2418 (1968).

¹⁴⁴ A. R. Burnett and R. H. Thomson, *J. Chem. Soc. C*, 850 (1968).

¹⁴⁵ M. Nakayama, S. Hayashi, M. Toukayama, T. Horie, and M. Masumura, *Chem. Lett.*, 315 (1972); *Chem. Abstr.* **77**, 5284 (1972).

¹⁴⁶ S. Yamada, F. Ono, T. Katagiri, and J. Tanaka, *Nippon Kagaku Kaishi*, 1987 (1972); *Chem. Abstr.* **78**, 16079 (1973).

fails,^{19,137,142,147} but no sure explanation has been provided so far. The participation of a 5-hydroxy substituent, that could assist giving a quinonemethide, has been suggested,^{142,4} but it contrasts with the successful dehydrogenation of unsubstituted chromanes.^{140,146} In rigid systems, such as tetrahydrocannabinols, stereoelectronic factors have been invoked to explain the course of the reaction.¹⁴³ The dehydrogenation of the 8-acetyl-5-hydroxychromane (35) gave the 6-acetyl-5-hydroxychromene (37).¹⁴⁸ This result might be explained with the sequence of Scheme 2, or with a similar one where the intermediate is a



SCHEME 2

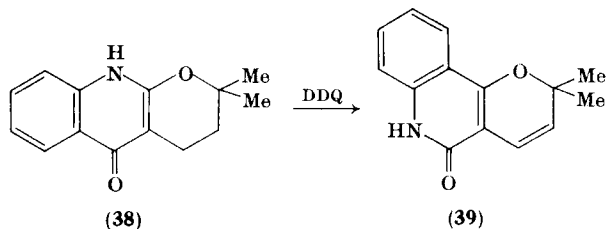
carbonium ion, but in both cases the driving force should be furnished by the newly formed hydrogen bond. A similar rearrangement occurs in the natural pigment rottlerin,³ which also is a 5-hydroxy-8-acylchromene. The only other example of this interesting rearrangement is the recent conversion of the alkaloid khaplofoline (38) into flindersine (39)¹⁴⁹ which adopts the preferred 2-quinolone structure.¹⁵⁰

¹⁴⁷ G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron* **27**, 1875 (1971).

¹⁴⁸ M. Nakayama, S. Nishimura, T. Matsui, S. Hayashi, and K. Fukui, *Nippon Kagaku Zasshi* **91**, 1092 (1970); *Chem. Abstr.* **75**, 20110 (1971).

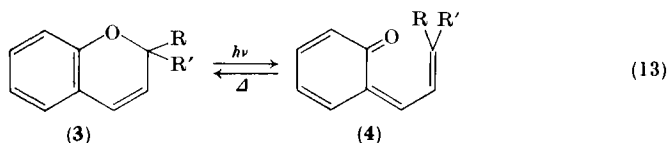
¹⁴⁹ L. Maat, A. W. Buijten van Weelderen, and H. C. Beyerman, *Rec. Trav. Chim.* **92**, 1399 (1973).

¹⁵⁰ R. M. Bowman, M. F. Grindon, and K. J. James, *Chem. Commun.*, 666 (1970); *J. Chem. Soc. Perkin Trans. 1*, 1055 (1973).



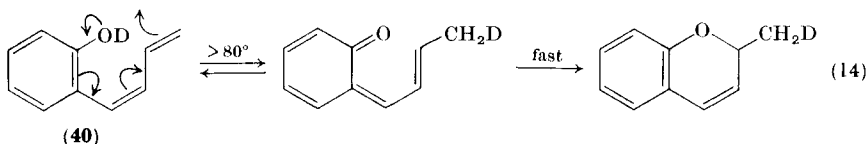
B. CYCLIZATION OF *ortho*-ALKYL PHENOLS AND DERIVATIVES

Chromenes (**3**) are valence tautomers of *o*-quinoneallides (**4**). Recent reports^{31,32,151} have demonstrated the photochemical opening of the



chromene ring [Eq. (13)]: the *o*-quinoneallides are unstable, and thermal recyclization occurs even at very low temperature. The open forms have been trapped (see Section II). Thus, if one assumes that the electrocyclic ring closure is an extremely facile process, any synthesis of *o*-quinoneallides becomes a synthesis of chromenes.^{152,153}

Thermal cyclization of butadienylphenols (**40**), which are prepared from salicylaldehyde and a Wittig reagent, has been shown to give chromenes.^{154,155} Deuteration confirmed the proposed mechanism, i.e., a [1,7] sigmatropic shift to a quinoneallide [Eq. (14)]. At temperatures



higher than 210°, the cyclization becomes reversible. The equilibrium is shifted toward the chromene, except for 2-benzylchromene, for which 45% of the corresponding *trans,trans*-butadienylphenol is present at 210°.

¹⁵¹ A. Padwa and G. A. Lee, *Chem. Commun.*, 795 (1972).

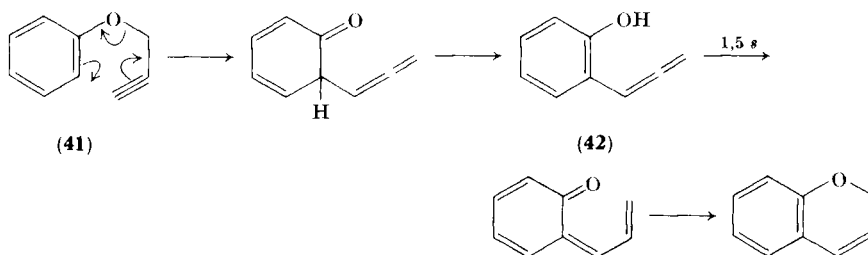
¹⁵² G. Cardillo, L. Merlini, and S. Servi, *Ann. Chim. (Rome)* **60**, 564 (1970).

¹⁵³ R. Hug, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **55**, 1675 (1972).

¹⁵⁴ R. Hug, H.-J. Hansen, and H. Schmid, *Chimia* **23**, 108 (1969); *Helv. Chim. Acta* **55**, 1828 (1972).

¹⁵⁵ E. E. Schweizer, D. M. Crouse, and D. L. Dalrymple, *Chem. Commun.*, 354 (1969).

The Claisen rearrangement of propargyl ethers of phenols (**41**) is one of the best syntheses of chromenes. The starting materials are easily prepared, and yields are usually up to 80% or more. This reaction was introduced in 1962 by Iwai and Ide,¹⁵⁶ who prepared many chromenes and studied the effects on yields of substituents in the aromatic ring. It was later applied to the synthesis of 4-substituted chromenes,¹⁵⁷ but only in 1968 Schmid and co-workers¹⁵⁸ formulated it correctly as a Claisen rearrangement, followed by a [1,5] sigmatropic shift (Scheme 3). 2-Allenylphenol itself (**42**) gives chromene by heating.¹⁵⁸ The reaction



SCHEME 3

has been extended to the synthesis of a large number of natural 2,2-dimethylchromenes,^{18,159} and has now found wide acceptance.¹⁶⁰⁻¹⁶⁹ Benzodipyrans and naphthodipyrans are obtained from bis ethers of quinol and 2,7-naphthalenediol.¹⁷⁰ Sometimes the chromene is formed

¹⁵⁶ I. Iwai and J. Ide, *Chem. Pharm. Bull.* **10**, 926 (1962); **11**, 1042 (1963).

¹⁵⁷ B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, *Tetrahedron* **23**, 1893 (1967); K. C. Majumdar and B. S. Thyagarajan, *J. Heterocycl. Chem.* **9**, 489 (1972).

¹⁵⁸ J. Zsindely and H. Schmid, *Helv. Chim. Acta* **51**, 1510 (1968).

¹⁵⁹ J. R. Hlubucek, E. Ritchie, and W. C. Taylor, *Tetrahedron Lett.*, 1369 (1969); *Aust. J. Chem.* **24**, 2347 (1971).

¹⁶⁰ J. A. Miller and H. C. S. Wood, British Patent 1,121,307 (1968); *Chem. Abstr.* **69**, 96471 (1968).

¹⁶¹ S. K. Mukerjee, S. C. Sarkar, and T. R. Seshadri, *Indian J. Chem.* **8**, 861 (1970).

¹⁶² P. S. Sampath Kumar, V. V. S. Murti, and T. R. Seshadri, *Indian J. Chem.* **9**, 1319 (1971).

¹⁶³ Y. Besace, I. Marszak, and J. Maisse, *Bull. Soc. Chim. Fr.*, 2275 (1971).

¹⁶⁴ F. Bohlmann and U. Bühmann, *Ber.* **105**, 863 (1972).

¹⁶⁵ J. W. Huffmann and T. M. Hsu, *Tetrahedron Lett.*, 141 (1972).

¹⁶⁶ A. J. Quillinan and F. Scheinmann, *J. Chem. Soc. Perkin Trans. 1*, 1382 (1972).

¹⁶⁷ M. Krishnamurthy, K. R. Sambhy, and T. R. Seshadri, *Indian J. Chem.* **10**, 914 (1972).

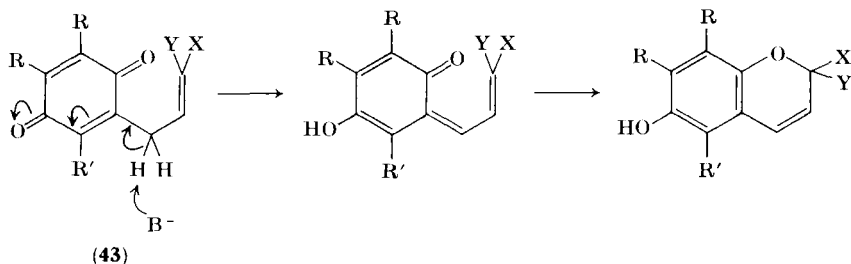
¹⁶⁸ F. Fujita, N. Nakatami, and M. Matsui, *Agr. Biol. Chem.* **37**, 1737 (1973).

¹⁶⁹ B. J. Bajwa, P. Lal, and T. R. Seshadri, *Indian J. Chem.* **9**, 17 (1971).

¹⁷⁰ K. K. Balasubramanian and B. Venugopalan, *Tetrahedron Lett.*, 2707 (1973).

already in the alkylation step.^{18,165,166} A remarkable stereospecificity has been observed,^{156,159} but in some cases of resorcinol derivatives both isomers are formed.^{161,169} These results have now been rationalized by considering the stability of the transition state leading to the dienone intermediate.¹⁷¹ When chelate or fused-ring stabilization compete for control of the regioselectivity, the formation of mixture can be foreseen (see later in this section). A detailed study of the substituent effect and of the increase in rate due to the gem-dimethyl effect has appeared recently.¹⁷² The use of *o,o*-dichlorobenzene instead of the usual *N,N*-dimethylaniline as solvent increased the yields.¹⁷² Catalysis by AgBF_4 or CF_3COOAg in benzene or chloroform has been discovered.¹⁷³ The silver ion rapidly forms a π -preequilibrium complex with the acetylenic ether, which undergoes the slow $[3s,3s]$ sigmatropic shift of the rearrangement, and also participates in the allenylphenol to chromene step, doubling its rate at room temperature. A similar effect is shown by mercuric ions.¹⁷⁴

Compounds at the same oxidation level of chromenes are *o*-isopentenylquinones (43). Their cyclization is obtained with bases, according to the mechanism of Scheme 4.¹⁷⁵ The first example of this



SCHEME 4

reaction dates back to Paternò,¹⁷⁶ who cyclized lapachol with sodium acetate. However, the presence of an additional OH in lapachol gives rise to ortho and para quinone isomers, so that the structure of the

¹⁷¹ D. G. Clarke, L. Crombie, and D. A. Whiting, *Chem. Commun.*, 580 (1973).

¹⁷² M. Harfenist and E. Thom, *J. Org. Chem.* **37**, 841 (1972).

¹⁷³ U. Koch-Pomeranz, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **56**, 2981 (1973).

¹⁷⁴ K. K. Balasubramanian, K. Virupaksha Reddy, and R. Nagarajan, *Tetrahedron Lett.*, 5003 (1973).

¹⁷⁵ B. O. Linn, C. H. Shunk, E. L. Wong, and K. Folkers, *J. Amer. Chem. Soc.* **85**, 239 (1963).

¹⁷⁶ E. Paternò, *Gazz. Chim. Ital.* **12**, 337 (1882); E. Paternò and G. Minunni, *ibid.* **19**, 607 (1889).

products was established only much later.¹⁴¹ The cyclization of ubiquinone [43, R = OMe, R' = Me, X = Me, Y = (CH₂CH = CMeCH₂)₉H] has been much studied, owing to the biological importance of such substances. Recent applications to many types of polyisoprenylquinones have been reported: bases include alumina,¹⁷⁷ NaOH,¹⁷⁸ NaH,^{96,175,179} pyridine,^{96,180,181} triethylamine.¹⁸² Quinones as simple as 2-allylquinone give the corresponding chromenes,¹⁸³ and dalbergiones cyclize to 4-phenylchromenes (neoflavones).¹⁸⁴⁻¹⁸⁶ Photochemical cyclization of ubiquinone¹⁸⁷ and of vitamin K¹⁸⁸ have also been obtained.

Another reaction which requires *o*-quinoneallides as intermediates is the synthesis of chromenes from benzyne and α,β -unsaturated aldehydes (Scheme 5).¹⁸⁹ The formation of the unstable benzoxete was confirmed by isotope labeling. Yields are in the range 4–40%.

The same quinoneallides are probably involved in the reaction of 3,3-dimethylallyltriphenylphosphorane with *o*-benzoquinones (Scheme 6),¹⁵² which gives chromenes, although in low yield.

The cyclodehydrogenation of 2-(3,3-dimethylallyl)phenols with DDQ or chloranil (Scheme 7) has been envisaged⁷⁷ on the basis of a biogenetic

¹⁷⁷ J. Links, *Biochim. Biophys. Acta* **38**, 193 (1960); J. Links and O. Tol, *ibid.* **73**, 349 (1963); C. H. Shunk, F. R. Koninszy, E. L. Wong, N. R. Trenner, B. H. Arison, and K. Folkers, *Biochem. Biophys. Res. Commun.*, **3**, 228 (1960); F. W. Hemming, R. A. Morton, and J. F. Pennock, *Biochem. J.* **80**, 445 (1961).

¹⁷⁸ H. H. Draper and A. S. Csallany, *Biochem. Biophys. Res. Commun.* **2**, 307 (1960).

¹⁷⁹ A. F. Wagner, P. E. Wittreich, B. Arison, N. R. Trenner, and K. Folkers, *J. Amer. Chem. Soc.* **85**, 1178 (1963).

¹⁸⁰ D. McHale and J. Green, *Chem. Ind. (London)*, 1867 (1962).

¹⁸¹ K. L. Stevens, L. Jurd, and G. Mannes, *Tetrahedron Lett.*, 2955 (1973).

¹⁸² I. Imada and H. Morimoto, *Chem. Pharm. Bull.* **13**, 130 (1965).

¹⁸³ D. McHale and J. Green, *J. Chem. Soc.*, 5060 (1965).

¹⁸⁴ W. D. Ollis, B. T. Redman, R. J. Roberts, I. O. Sutherland, and O. R. Gottlieb, *Chem. Commun.*, 1392 (1968); W. D. Ollis, in "Recent Advances in Phytochemistry" (J. T. Mabry *et al.* eds.), Vol. 2, p. 328. Appleton, New York, 1968.

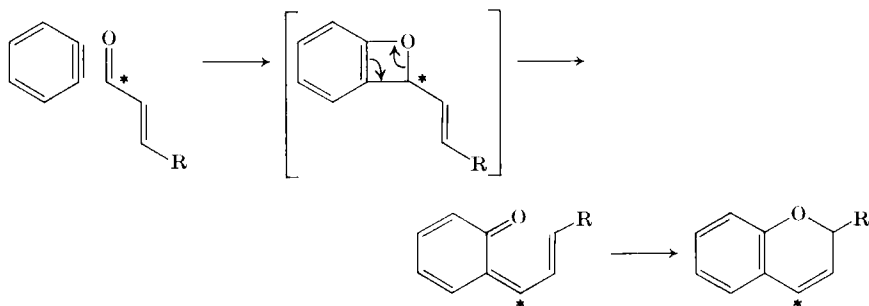
¹⁸⁵ S. K. Mukerjee, T. Saroja, and T. R. Seshadri, *Tetrahedron* **27**, 799 (1971).

¹⁸⁶ D. M. X. Donnelly, P. J. Kavanagh, G. Kunesch, and J. Polonsky, *J. Chem. Soc. Perkin Trans. 1*, 965 (1973).

¹⁸⁷ H. Morimoto and I. Imada, *Chem. Pharm. Bull.* **12**, 739, 1042 (1964); H. W. Moore and K. Folkers, *Ann.* **684**, 212 (1965); H. M. Cheng and J. E. Casida, *J. Label. Compounds* **6**, 67 (1970).

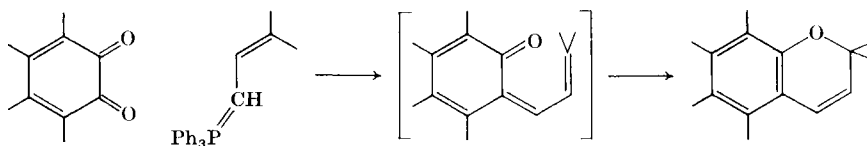
¹⁸⁸ S. Fujisawa, S. Kawabata, and R. Yamamoto, *Yakugaku Zasshi* **87**, 1451 (1967); *Chem. Abstr.* **69**, 35874 (1968).

¹⁸⁹ H. Heaney and J. M. Jablonski, *Chem. Commun.*, 1139 (1968); H. Heaney, J. M. Jablonski, and C. T. McCarty, *J. Chem. Soc. Perkin Trans. 1*, 2903 (1972).



SCHEME 5

hypothesis^{65,68} and has been extended to a series of natural chromenes^{140,143} and flavenes.¹⁹⁰ Yields rarely exceed 50%, but the method has found wide application^{18,57,135,150,162,169,191-204} especially in the conversion of naturally occurring isopentenylphenols into chromenes. The first step is supposed to be the abstraction of an hydride ion from the benzylic position, which leads to a quinoneallide (see Scheme 1).



SCHEME 6

¹⁹⁰ G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron Lett.*, 907 (1969).

¹⁹¹ K. H. Dudley and R. W. Chiang, *J. Org. Chem.* **34**, 120 (1969).

¹⁹² G. Cardillo, R. Cricchio, L. Merlini, and G. Nasini, *Gazz. Chim. Ital.* **99**, 308 (1969).

¹⁹³ A. C. Jain, P. Lal, and T. R. Seshadri, *Indian J. Chem.* **7**, 1072 (1969).

¹⁹⁴ S. Nozoe and K. T. Suzuki, *Tetrahedron Lett.*, 2457 (1969).

¹⁹⁵ K. R. Bala and T. R. Seshadri, *Phytochemistry* **10**, 1131 (1971).

¹⁹⁶ B. S. Bajwa, P. L. Khanna, and T. R. Seshadri, *Indian J. Chem.* **9**, 1322 (1971).

¹⁹⁷ A. C. Jain and S. M. Jain, *Tetrahedron* **28**, 981 (1972); S. M. Anand and A. C. Jain, *ibid.* **28**, 987 (1972); A. C. Jain and S. M. Jain, *Tetrahedron Lett.*, 759 (1972); *Tetrahedron* **28**, 5063 (1972); *ibid.* **29**, 2803 (1973).

¹⁹⁸ R. A. Finnegan and R. E. Merkel, *Lloydia* **32**, 522 (1969).

¹⁹⁹ A. C. Jain and T. R. Seshadri, *Tetrahedron* **26**, 1977 (1970); A. C. Jain, V. K. Khanna, P. Lal, and T. R. Seshadri, *Indian J. Chem.* **8**, 480 (1970).

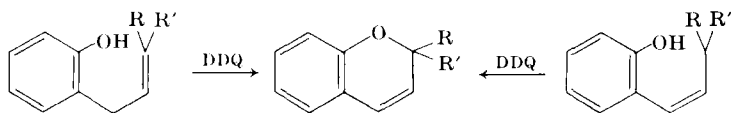
²⁰⁰ V. M. Deshpande, A. V. Rama Rao, B. Srinivasan, and K. Venkataraman, *Indian J. Chem.* **10**, 681 (1972).

²⁰¹ F. Delle Monache, O. Gonçalves de Lima, J. F. de Mello, G. Delle Monache, and G. B. Marini-Bettolo, *Gazz. Chim. Ital.* **103**, 779 (1973).

²⁰² J. L. Montero and F. Winteritz, *Tetrahedron* **29**, 1243 (1973).

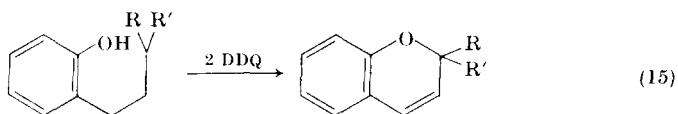
²⁰³ A. C. Jain and M. K. Zutshi, *Aust. J. Chem.* **26**, 641 (1973).

²⁰⁴ W. Steck, *Can. J. Chem.* **49**, 2297 (1971).

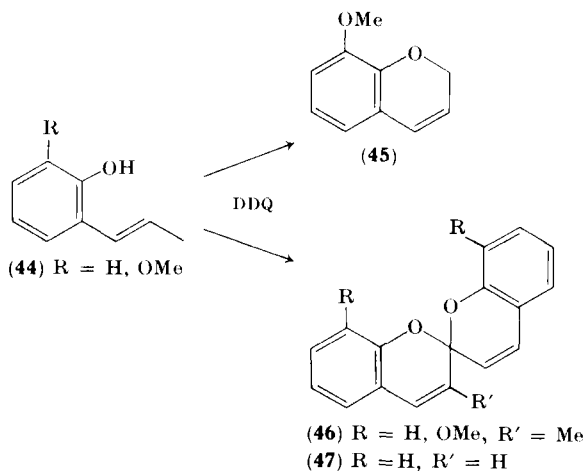


SCHEME 7

The reaction is successful only if R and R' are both alkyl, or when R = H and R' = Ph, but it can be performed also on α,β -unsaturated alkylphenols (Scheme 7) and on alkylphenols [Eq. (15)].¹⁴⁷ Depending on the conditions, *o*-propenylphenols (**44**) give the chromene (**45**)²⁰⁵



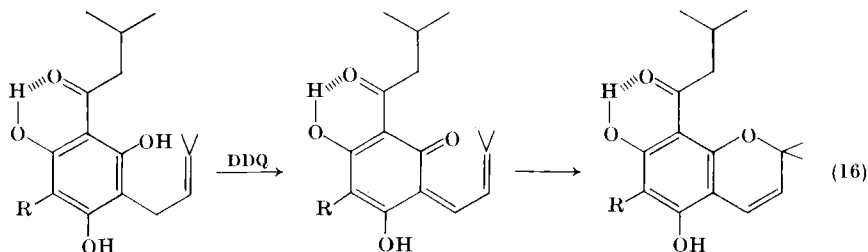
or the spiropyrans (**46**),¹⁴⁷ most probably via a vinylogous nucleophilic attack of one molecule of **44** on the *o*-quinoneallide, followed by two



dehydrogenative steps. Consistently with this hypothesis, **47** has also been obtained by DDQ treatment of 1,5-bis-(2-hydroxyphenyl)-1,4-pentadiene.²⁰⁵ A strong influence of the solvent on the product of the reaction has been observed.¹⁴⁷ A neat regiospecific effect is observed when there is choice, usual in the synthesis of natural products, of ring closure onto a free or a chelated hydroxyl. The chelated hydroxyl never reacts, except when the chelation is loosened by another hydroxyl

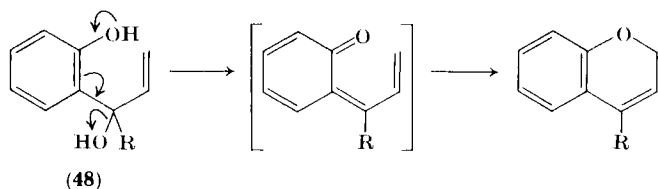
²⁰⁵ L. Merlini and co-workers, unpublished.

ortho to the carbonyl group. So far, reports of this last effect concern only compounds where there is a 2-methylpropanoyl or a 3-methylbutanoyl group between two OH, such as in the synthesis of mammeigin from mammeisin^{57,195,198} or of the antibiotic uliginosin B.²⁰⁶ In this

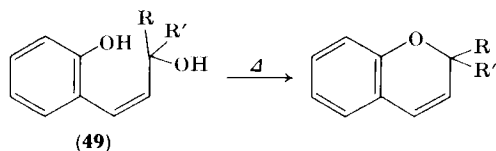


latter compound, the unusually strong specific chelation is substantiated by X-ray analysis.⁹ The unexpected formation of only one isomer [Eq. (16)] in this case is a good support for Crombie and Whiting's theory¹⁷¹ of the regiospecificity of this and other related reactions, which requires the formation of the frequently postulated quinonemethide intermediate.^{68,77,140,147} The formation of the isomeric quinonemethide, involving the OH in 4, would mean the loss of the chelate stabilization (see also later, this section).

The ubiquitous *o*-quinoneallides appear again in the thermal 1,4-elimination of water from *o*-hydroxyphenylallyl alcohols (48),¹⁵³



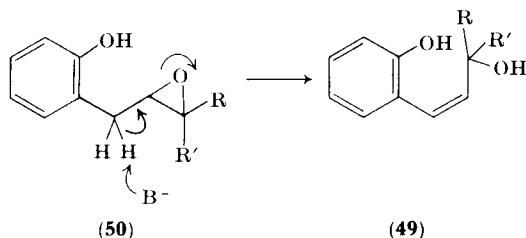
which have now become easily available from salicylaldehyde or *o*-hydroxyacetophenones and a vinylmagnesium halide. The same mechanism probably plays a role in the similar pyrolysis of *o*-hydroxycinnamyl alcohol (49, R = R' = H), which, already employed to prepare the parent chromene,²⁰⁷ has been extended to the substituted alcohols



²⁰⁶ T. Meikle and R. Stevens, *Tetrahedron Lett.*, 4787 (1972).

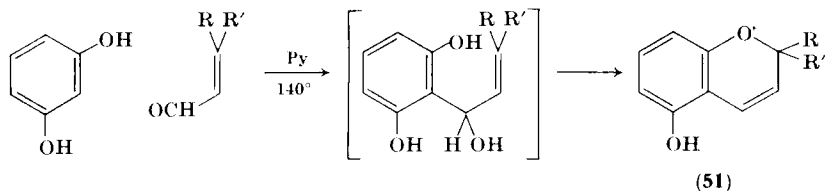
²⁰⁷ J. N. Chatterjea, *J. Indian Chem. Soc.* **36**, 76 (1959).

(49, $R = R' = \text{Me}$) which are obtained by photooxidation of the corresponding olefin.⁷² The acid-induced cyclization of the same alcohols has been used: they are prepared from coumarins^{87,88,185,186} or by base-promoted elimination from epoxides (50).^{150,164} The acid-catalyzed equilibrium between these alcohols and the corresponding



benzylic alcohols (48) has been shown to exist.⁸⁹ These latter, which are acid-sensitive and prone to disproportionation, are also obtained by NaBH_4 reduction of the ketones.⁸⁹ In the reduction of 2-hydroxychalcones, they were not isolated, but immediately cyclized: this is one of the simplest syntheses of flavenes.^{29,208,209}

The benzylic alcohols (48) are probable intermediates in another very good synthesis, the condensation of α,β -unsaturated aldehydes with resorcinols in the presence of pyridine (Scheme 8).²¹⁰⁻²¹³ Advantages of this procedure are the high yields and the use of the easily accessible 3-methyl-3-hydroxybutyraldehyde dimethylacetal²¹⁴ instead of the unstable 3,3-dimethylacrolein. The method has been particularly useful



SCHEME 8

²⁰⁸ J. W. Clark-Lewis, R. W. Jemison, D. C. Skingle and L. R. Williams, *Chem. Ind. (London)*, 1455 (1967); J. W. Clark-Lewis and D. C. Skingle, *Aust. J. Chem.* **20**, 2169 (1967); J. W. Clark-Lewis and R. W. Jemison, *ibid.* **21**, 2247 (1968).

²⁰⁹ T. Hase, *Acta Chem. Scand.* **22**, 2845 (1968).

²¹⁰ L. Crombie and R. Ponsford, *J. Chem. Soc. C*, 788 (1971).

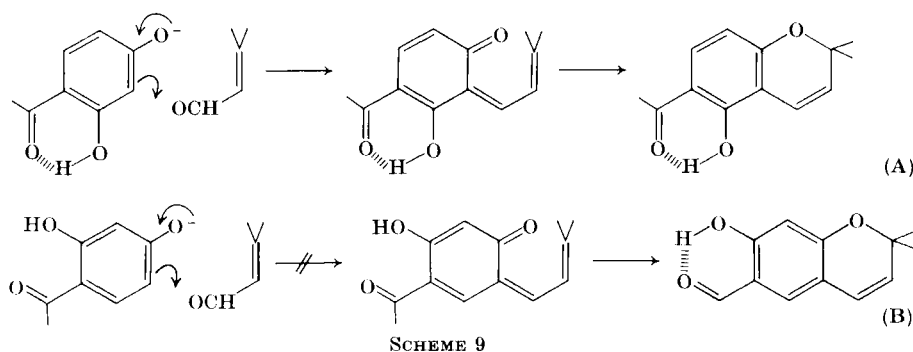
²¹¹ L. Crombie and R. Ponsford, *J. Chem. Soc. C*, 796 (1971).

²¹² L. Crombie, W. M. Bandaranayake, and D. A. Whiting, *J. Chem. Soc. C*, 804 (1971).

²¹³ V. V. Kane and R. K. Razdan, *J. Amer. Chem. Soc.* **90**, 6551 (1968).

²¹⁴ L. Crombie, W. M. Bandaranayake, and D. A. Whiting, *J. Chem. Soc. C*, 811 (1971).

in the synthesis of a series of C_{10} derivatives (**51**, $R = Me$, $R' = CH_2CH=CHMe$), starting from citral. The cyclization may occur via ring closure by elimination of water; or through an *o*-quinoneallide.²¹¹ A different mechanism, involving a Michael addition of the phenol on the aldehyde, has been proposed.²¹⁵ The formation of the intermediate quinoneallide has now been emphasized, as it provides the rationalization for the regiospecificity of the reaction.¹⁷¹ When one of the hydroxyls is chelated, the chromenylation, being triggered by the acidic, unchelated OH, occurs at the position such as to allow retention of the stabilization energy of the chelate (Scheme 9, orientation A, *not* B). A



SCHEME 9

number of examples, including cases where the conflict between retention of the stabilization energy of the chelate and that of a fused ring explains the formation of mixtures, support this interpretation¹⁷¹ (see also above, this section). The only example of the use of ketones concerns the reaction between mesityl oxide and 4-hydroxycoumarin.²¹⁹ Other successful applications have been reported,^{55,61,202,216-218} but the reaction has failed so far with simple phenols or quinols.²¹⁴

A similar pathway was followed in the synthesis of siccanochromenes (e.g., **17**), where the aldehyde was condensed with the lithio derivative of a protected resorcinol. Treatment with oxalic acid gave directly the chromene in 45% yield.²²⁰

More complicated from a mechanistic point of view is the recent

²¹⁵ V. Kane and T. Grayeek, *Tetrahedron Lett.*, 3991 (1971).

²¹⁶ W. J. G. Donnelly and P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 1*, 25 (1972).

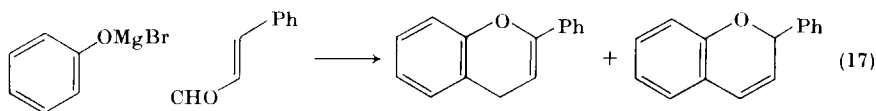
²¹⁷ J. R. Lewis and J. B. Reary, *J. Chem. Soc. C*, 1662 (1970).

²¹⁸ G. Combes, J. C. Montero, and F. Winternitz, *C.R. Acad. Sci., Ser. C*, **274**, 1313 (1972).

²¹⁹ D. W. Hutchinson and J. A. Tomlinson, *Tetrahedron Lett.*, 5027 (1968).

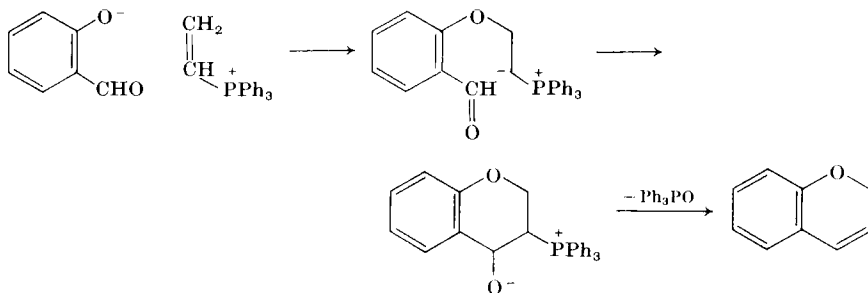
²²⁰ S. Nozoe and K. Hirai, *Tetrahedron* **27**, 6073 (1971).

synthesis of flavenes from cinnamaldehyde and phenoxymagnesium bromide [Eq. (17)].²²¹ A mixture of flav-2-ene and flav-3-ene is obtained but the latter rearranges to the former on further treatment with the Grignard reagent.



C. FROM SALICYLALDEHYDE

A series of papers by Schweizer's group²²²⁻²²⁴ has indicated the possibility of a general synthesis of chromenes in high yield by addition of the phenolate anion of salicylaldehyde to a vinylphosphonium salt



SCHEME 10

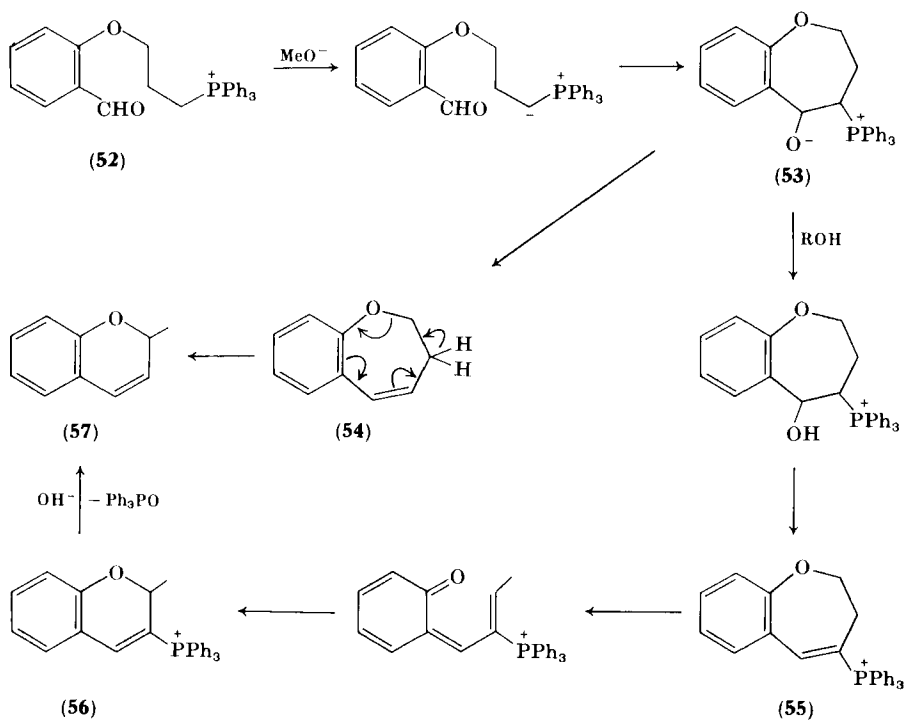
and subsequent Wittig reaction (Scheme 10). When an *o*-formylphenoxy trimethylenephosphonium salt (**52**) reacts with a base, the benzoxepin (**54**) or the chromene (**57**) are formed depending on the solvent used. In aprotic solvents the Wittig betaine (**53**) eliminates Ph₃PO to give the seven-membered compound. In protic solvents, such as alcohols, protonation of the anion occurs, and elimination of water gives the benzoxepin phosphonium derivative (**55**). This undergoes ring-opening, exactly as in the parent compound (**54**),¹⁵⁵ followed by electrocyclic ring closure to the chromene derivative (**56**). The same results, due to the same intermediates, are obtained when salicylaldehyde sodium salt

²²¹ G. Casiraghi, G. Casnati, and G. Salerno, *J. Chem. Soc. C*, 2546 (1971).

²²² E. E. Schweizer, *J. Amer. Chem. Soc.* **86**, 2744 (1964); E. E. Schweizer, J. Liehr, D. J. Monaco, *J. Org. Chem.* **33**, 2416 (1968).

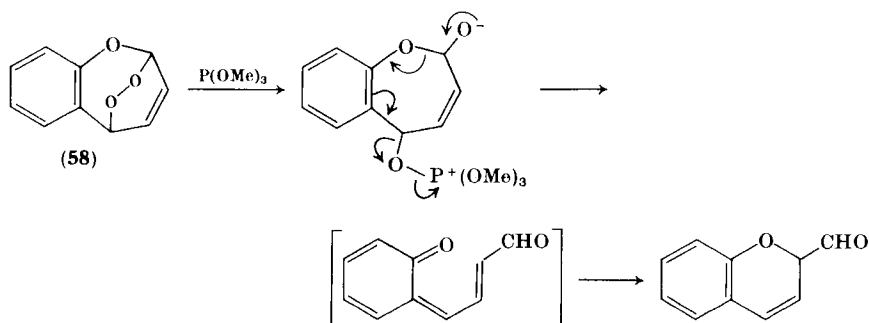
²²³ E. E. Schweizer, T. Minami, and D. M. Crouse, *J. Org. Chem.* **36**, 4028 (1971) and preceding papers; E. E. Schweizer, A. T. Wehman, and D. M. Nycz, *ibid.* **38**, 1583 (1973).

²²⁴ E. E. Schweizer, C. J. Berninger, and J. G. Thompson, *J. Org. Chem.* **33**, 336 (1968).



reacts with cyclopropyltriphenylphosphonium salts.²²⁴ Notwithstanding the high yields, the synthesis has been used rarely.²²⁵

A similar rearrangement occurs when the endoperoxide (58) is treated with P(OMe)_3 (Scheme 11).²²⁶



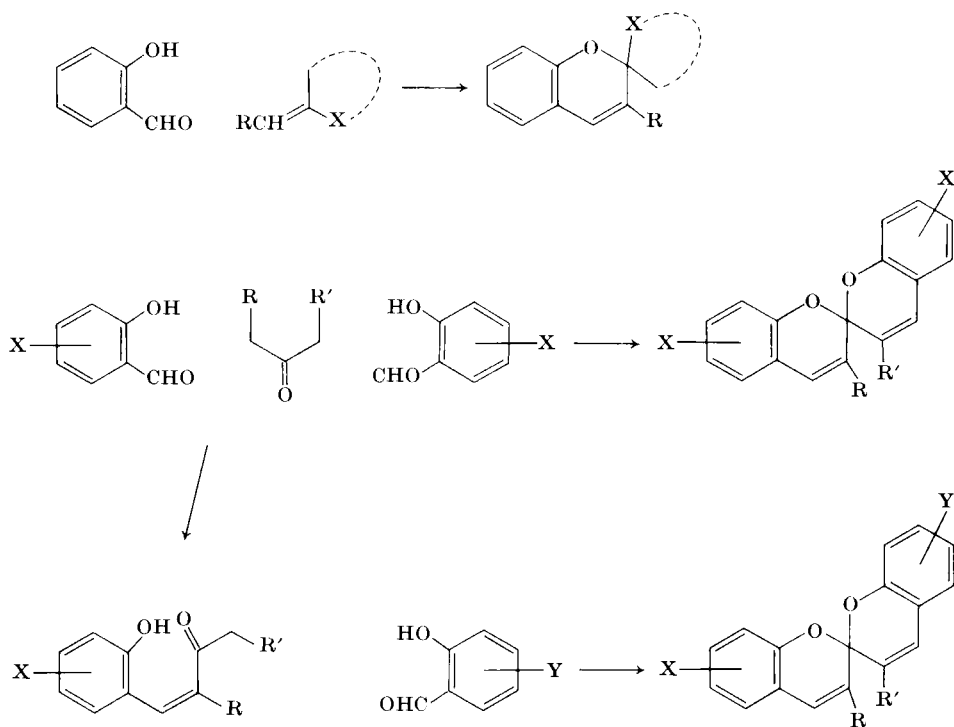
SCHEME 11

²²⁵ N. S. Narasimhan, M. V. Paradkar, and A. M. Gokhale, *Tetrahedron Lett.*, 1665 (1970).

²²⁶ J. E. Baldwin and O. W. Lever, *Chem. Commun.*, 344 (1973).

Condensation of salicylaldehydes with 2-chloro-3-formylbutene and analogs gave 2-methylenechromene derivatives.²²⁷ The direct reaction of salicylaldehyde with 2-methyl-2-chlorobutane or 2-methylbutene with catalysts to give 2,2,3-trimethylchromene is reported in a patent²²⁸ The structure of the products from salicylaldehyde and diphenylenes^{229,230} has been revised. (see Section V,B).²³¹

Salicylaldehyde is the starting material for the preparation (Scheme 12) of most spirobenzopyrans, which are important photochromic compounds. The reader interested in their synthesis and properties is referred to the recent excellent book by Bertelson.⁵



SCHEME 12

²²⁷ M. Weissenfels, P. Schneider, D. Schmiedl, and H. Altmann, *Z. Chem.* **12**, 263 (1972).

²²⁸ J. T. Arrigo, U.S. Patent 2,987, 525 (1961); *Chem. Abstr.* **56**, 3460 (1962).

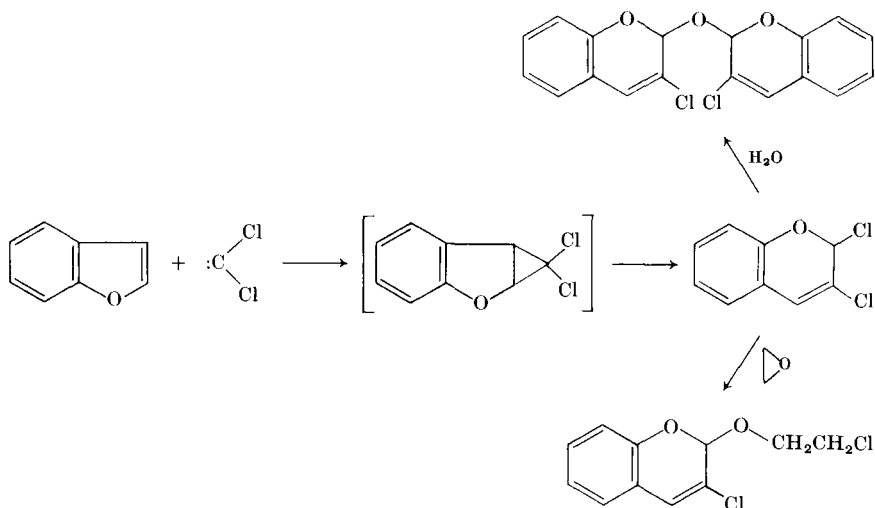
²²⁹ R. Wizinger, *Angew. Chem.* **52**, 383 (1959).

²³⁰ D. Abson, K. D. Bartle, J. Bryant, R. Livingstone, and R. B. Watson, *J. Chem. Soc.*, 2978 (1965).

²³¹ W. D. Cotterill, E. Bradley, R. Livingstone, and M. Walshaw, *J. Chem. Soc. C*, 3028 (1971) and refs. quoted therein.

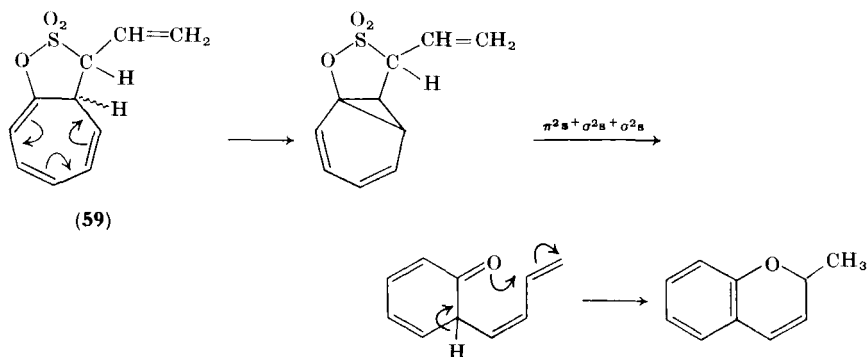
D. MISCELLANEOUS SYNTHESSES

The ring expansion of furans by dichlorocarbene addition gives unstable 2,3-dichlorochromenes, which are trapped by nucleophilic displacement reactions (Scheme 13).^{232,233}



SCHEME 13

A fascinating rearrangement ending into chromenes is the thermally allowed disrotatory $(4n + 2)\pi$ closure of the sultone (59) to a non-



SCHEME 14

²³² W. E. Parham, C. G. Fritz, R. W. Soeder, and R. M. Dodson, *J. Org. Chem.* **28**, 577 (1963).

²³³ F. Nerdel, J. Buddrus, W. Brodowski, P. Hentschel, D. Klamann, and P. Weyerstahl, *Justus Liebigs Ann. Chem.* **710**, 36 (1967).

isolated tricyclic intermediate, which loses SO_2 (Scheme 14).²³⁴ Compound **59** is obtained from tropone and allylsulfonylchloride in the presence of triethylamine.

V. Reactions

In general the reactions of chromenes are those expected from styrenes.³ Perhaps for this reason little attention has been paid to their chemical behaviour in recent years.

Hydrogenation to chromanes, oxidative degradation, and oxidation to pyrylium salts in acid medium have been known for a long time.³ A series of substituted benzopyrylium salts has been recently prepared by oxidation of chromenes with tritylium perchlorate.⁹⁷ Oxidation of 4-phenylchromenes to coumarins with CrO_3 -pyridine complex or with SeO_2 in dioxan has been reported.¹⁸⁶

A. ADDITIONS TO THE DOUBLE BOND

Osmium tetroxide^{3,92,235} or permanganate²³⁵ treatment of chromenes affords 3,4-*cis*-chromanediols, which are converted into the trans isomers by aqueous phosphoric acid at reflux.⁹² Flavenes give 2,3-*trans*-3,4-*cis*-flavandiols.²⁰⁸ Further oxidation to 3-hydroxychroman-4-one occurs with OsO_4 - KIO_4 mixed reagent.²³⁶ The epoxide²³⁷ or the *cis*-diol¹²² are obtained by action of peroxyacids on flavenes.

Bromination or chlorination gives 3,4-dihalo derivatives in good yield.²³⁸⁻²⁴³ Spontaneous dehydrobromination to 4-bromochromenes can, however, occur,²³⁸ especially in 7-methoxy derivatives.²³⁹ Flavene gives a mixture of 2,3-*trans*-3,4-*trans*-dibromoflavan and of 2,3-*cis*-3,4-*trans*-dibromoflavan, and this is assumed to be a proof of a bromonium

²³⁴ W. E. Truce and C. M. Lin, *J. Amer. Chem. Soc.* **95**, 4426 (1973).

²³⁵ F. Baranton, G. Fontaine, and P. Maitte, *C.R. Acad. Sci., Ser. C*, **264**, 410 (1967).

²³⁶ P. Cohen and P. Mamont, *Bull. Soc. Chim. Fr.*, 1164 (1967).

²³⁷ A. Nitta, *Yakugaku Zasshi* **88**, 816 (1968); *Chem. Abstr.* **70**, 37604 (1969).

²³⁸ R. Livingstone, D. Miller, and S. Morris, *J. Chem. Soc.*, 3094 (1960).

²³⁹ J. D. Hepworth and R. Livingstone, *J. Chem. Soc. C*, 2013 (1966).

²⁴⁰ B. J. Bolger, K. G. Marathe, E. M. Philbin, T. S. Wheeler, and C. P. Lillya, *Tetrahedron* **23**, 341 (1967).

²⁴¹ J. Cottam, R. Livingstone, and S. Morris, *J. Chem. Soc.*, 5266 (1965).

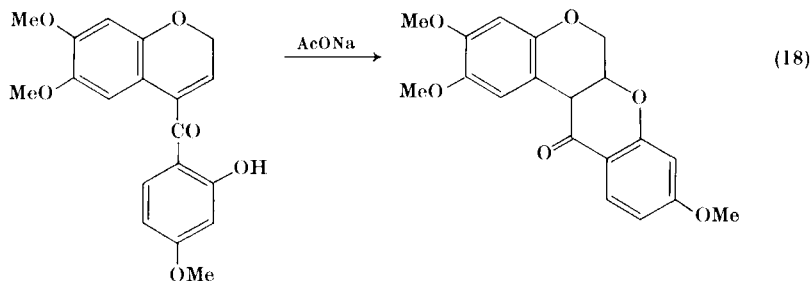
²⁴² J. B. Abbott, C. J. France, R. Livingstone, and D. P. Morrey, *J. Chem. Soc. C*, 1472 (1967).

²⁴³ D. Anker, J. Andrieux, M. Baran-Marszak, and D. Molho, *C.R. Acad. Sci., Ser. C* **274**, 650 (1972).

ion as intermediate.²⁴⁰ *N*-Bromosuccinimide in sulfuric acid gives the corresponding pair of 4-bromo-3-hydroxyflavans.²⁴⁰

Hydroboration of chrom-3-ene, followed by H_2O_2 oxidation, gives predominantly chroman-4-ol, with little 3-isomer.²⁴⁴ The same happens for flavene, which gives α -flavan-4-ol,¹²² but when the aromatic ring bears electron-releasing substituents, boration occurs preferably at position 3.²⁴⁵

2,4-Dinitrophenylhydrazine adds to the double bond in the presence of acids, but immediate dehydrogenation, apparently due to the nitro group, takes place, giving 4-phenylazochromanes as final products.²⁴⁶ Addition of $PhHgCl$ in the presence of Li_2PdCl_4 , followed by water-acetone treatment, gives 61% of *trans*-3-phenyl-4-hydroxychromane and a small amount of the *cis* isomer.²⁴⁷ The addition of Grignard reagents to 2-dicyanomethylenechromene affords 2-dicyanomethylene-4-alkylchromanes.²⁴⁸ A nucleophilic addition by the OH group of a phenol occurs in the synthesis of munduserone [Eq. (18)].²⁴⁹



The addition of carbenes has attracted some attention. Chromene, 2-alkyl and 4-ethoxychromenes react easily with dihalocarbenes^{99,250-252} generated by standard methods, to give in 50–80% yield dihalocyclopropa[*c*]chromenes, which can be reductively dehalogenated with sodium and alcohol.^{250,251} Thermal homoelectrocyclic ring opening,

²⁴⁴ J. W. Clark-Lewis and E. J. McGarry, *Aust. J. Chem.* **26**, 819 (1973).

²⁴⁵ J. W. Clark-Lewis and E. J. McGarry, *Aust. J. Chem.* **26**, 809 (1973).

²⁴⁶ R. Livingstone and R. B. Watson, *J. Chem. Soc.*, 1509 (1957).

²⁴⁷ M. Arai, K. Kabuto, H. Horino, and N. Inoue, *Chem. Lett.*, 889 (1972); *Chem. Abstr.* **77**, 164397 (1972).

²⁴⁸ N. Latif, I. Zeid, and F. Asaad, *Chem. Ind. (London)*, 1539 (1970).

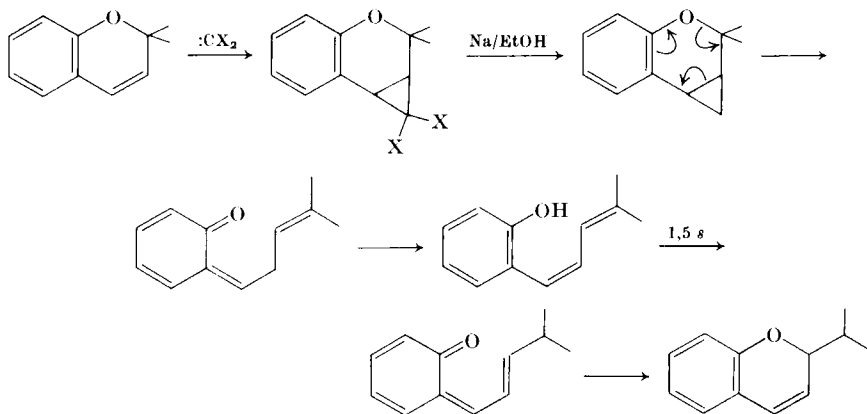
²⁴⁹ H. Omokawa and K. Yamashita, *Agr. Biol. Chem.* **37**, 195 (1973).

²⁵⁰ C. Marcaillou, G. Fontaine, and P. Maitte, *C.R. Acad. Sci., Ser. C* **267**, 846 (1968).

²⁵¹ R. Hug, G. Frater, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 306 (1971).

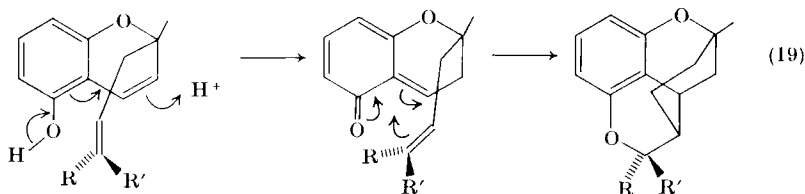
²⁵² M. C. Jacquet, B. Graffe, and P. Maitte, *Bull. Soc. Chim. Fr.*, 2557 (1971).

followed by sigmatropic shifts, leads to the 2-homologated chromene (Scheme 15).²⁵¹ The rate of rearrangement is remarkably dependent on the stereochemistry of the cyclopropa[*c*]chromenes (cis or trans to the 2 substituent).²⁵¹ In the cis compound, considerable steric hindrance appears in the disrotatory opening step.



SCHEME 15

A particular case of addition to the double bond is the so-called "citrylidene cyclization."²¹⁰ When 5-hydroxychromenes derived from citral are heated in pyridine, they cyclize to "citrylidene compounds" [Eq. (19)]. The electrocyclic mechanism, recently proposed,²⁵³ accounts



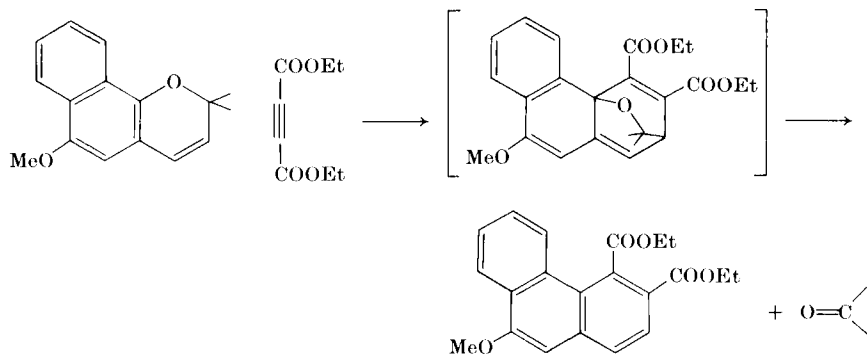
better than a previous one²¹⁰ for the stereoselectivity of the reaction. The method is useful in the synthesis of natural compounds, such as bruceol.²¹⁰

The photoaddition of phenanthrenequinone to the double bond of 2,2-dimethylchromene gives a mixture of a ketooxetane (1,2-addition, 38%) and of a 1,4-dioxene (1,4-addition, 25%).^{253a}

²⁵³ D. G. Clarke, L. Crombie, and D. A. Whiting, *Chem. Commun.*, 582 (1973).

^{253a} C. H. Krauch, S. Farid, and G. O. Schenck, *Ber.* **98**, 3102 (1965).

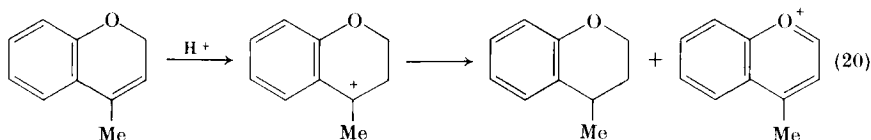
The only reaction in which a chromene appears to react as a heterodiene and not like a styrene is the addition of acetylene dicarboxylate to lapachenol, followed by thermal decomposition of the adduct (Scheme 16).²⁵⁴ The ready photodimerization of a chromene has been reported recently.²⁵⁵ (See also cannabicycol, Section V,B.)



SCHEME 16

B. REACTIONS IN THE PRESENCE OF ACIDS

Protonation of 4-methylchromene by strong acids gives a carbonium ion, which can disproportionate by hydride ion transfer to form 4-methylenechromane and the pyrylium salt [Eq. (20)].²⁵⁶



The structures of the so-called 2,2-dimethylchromene and 2,2-diphenylchromene dimers have been much debated. In 1900 Manuelli²⁵⁷ discovered that the natural compound lapachenol, to which later²⁵⁸ the structure **60** was assigned, gave a dimeric product by treatment with acids. On the basis of a mechanistic suggestion of Woodward, Living-

²⁵⁴ W. Sandermann and R. Casten, *Tetrahedron Lett.*, 1267 (1963); see also B. A. Otter, S. S. Saluja, and J. J. Fox, *J. Org. Chem.* **37**, 2858 (1972).

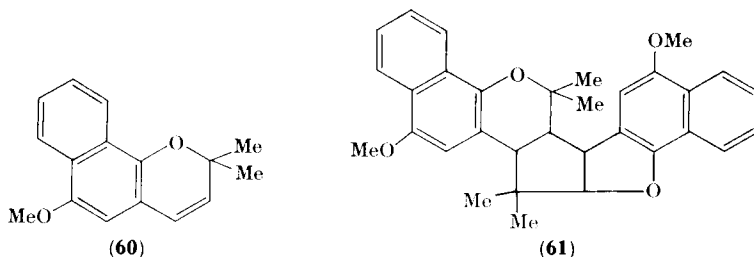
²⁵⁵ R. Braz Filho, M. de J. Coutinho Lemos, and O. R. Gottlieb, *Phytochemistry* **12**, 947 (1973).

²⁵⁶ B. D. Tilak and Z. Muljani, *Tetrahedron* **24**, 949 (1968).

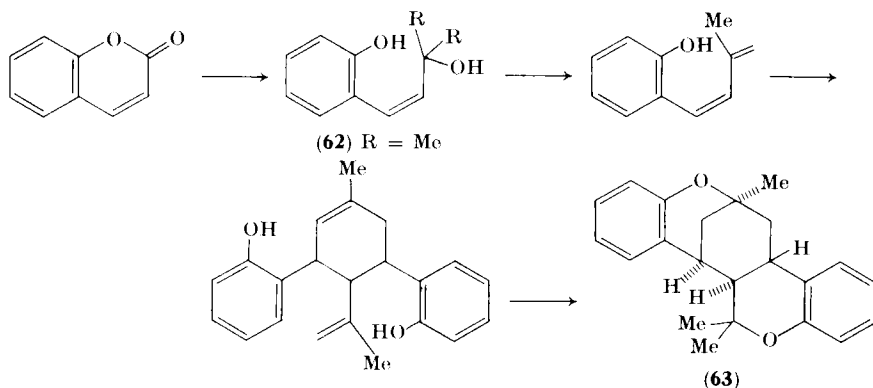
²⁵⁷ C. Manuelli, *Atti Accad. Naz. Lincei* **9**, 102, 314 (1900); **22**, 686 (1913).

²⁵⁸ R. Livingstone and M. C. Whiting, *J. Chem. Soc.*, 3631 (1955).

stone and Whiting²⁵⁸ assigned the structure **61** to this dimer. This formulation was deemed unlikely by Barnes, Strong, and Oecolowitz,²⁵⁹



who investigated the so-called 2,2-dimethylchromene dimer. They assigned the structure and stereochemistry (**63**) to the latter on the basis of NMR evidence, and attributed the same skeleton, by analogy, to lapachenol dimer. The mechanism which was proposed accounts for the fact that 2,2-dimethylchromene dimer (**63**) is not obtained from the chromene itself, but only by reaction of coumarin with MeLi or MeMgX. As, however, lapachenol dimer can be prepared directly from the chromene, not from the carbinol corresponding to (**62**), the Australian authors' contention concerning its structure deserved further proof.

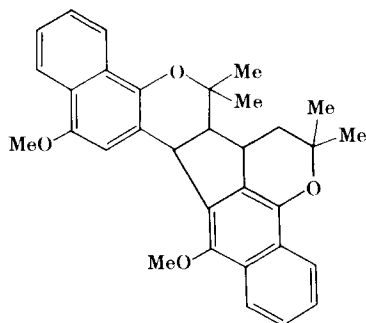


The structure (**64**) has now been suggested, on the basis of NMR and deuteration experiments, and a reasonable mechanism formulated.²⁶⁰ The same mechanism (Scheme 17) explains the formation of the dimer of ageratochromene with various acids.²⁶¹ Iodine in acid-free chloroform yields instead the dimer (**65**).²⁶¹

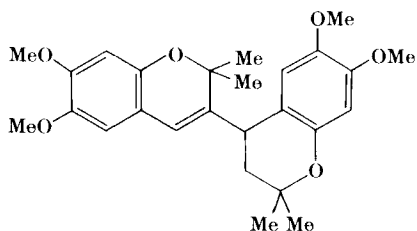
²⁵⁹ C. S. Barnes, M. I. Strong, and J. L. Oecolowitz, *Tetrahedron* **19**, 839 (1963).

²⁶⁰ W. D. Cotterill, R. Livingstone, K. D. Bartle, and D. W. Jones, *Tetrahedron* **24**, 1981 (1968).

²⁶¹ T. R. Kasturi, E. M. Abraham, and P. Brown, *J. Chem. Soc. Perkin Trans. 1*, 2468 (1973).

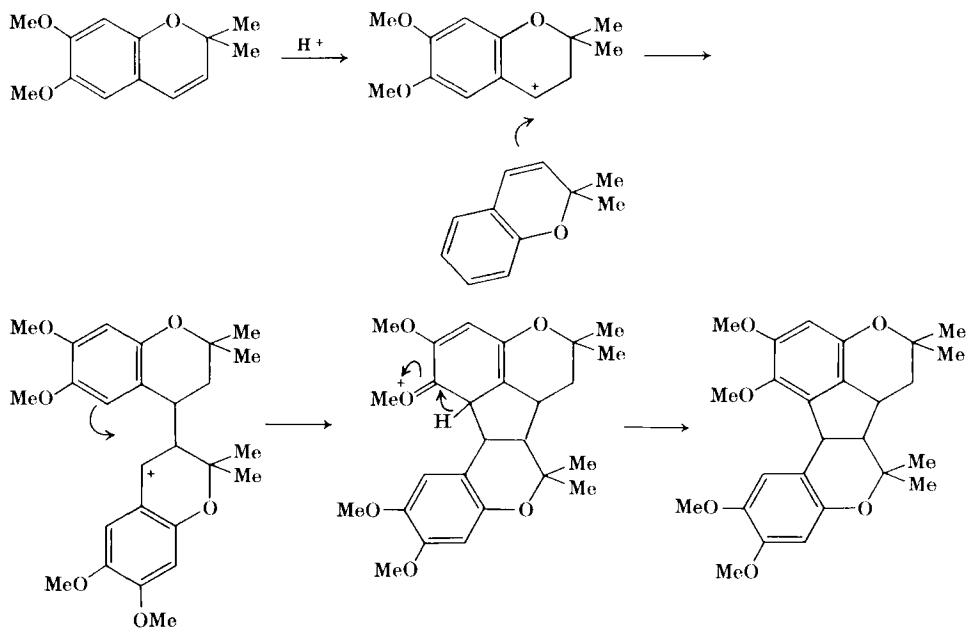


(64)



(65)

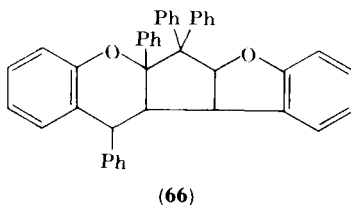
The so-called 2,2-diphenylchromene dimer (again the name is misleading) is obtained in the reaction of coumarin with C_6H_5MgBr , or from the carbinol (**62**, $R = Ph$). In this case the mechanism that requires the dehydration of the carbinol is not possible, and structure (**66**) has been proposed on the basis of the NMR spectrum.²⁶² This



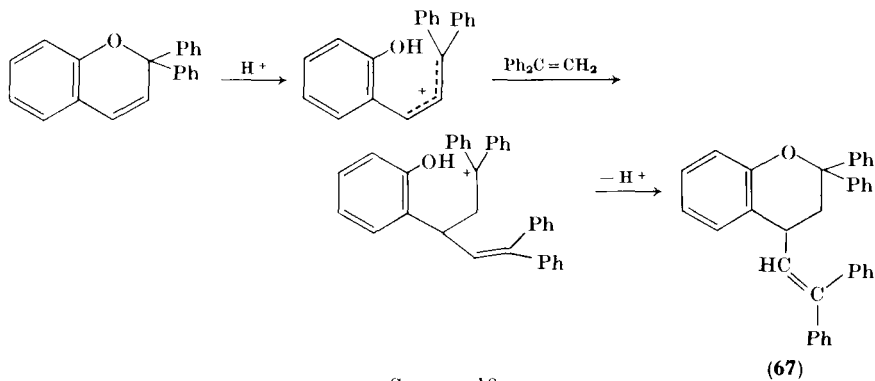
SCHEME 17

²⁶² J. Cottam, R. Livingstone, M. Walshaw, K. D. Bartle, and D. W. Jones, *J. Chem. Soc.*, 5261 (1965).

structure also explains the formation of **66** from a mixture of 2,2-diphenylchromene and 2,4-diphenylchrom-2-ene in acetic acid saturated with HCl. Another difficult problem has been the structural elucidation



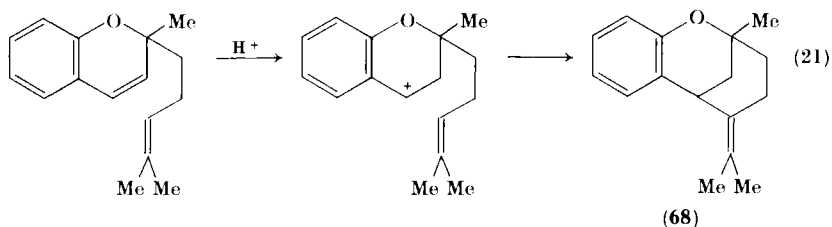
of the product of the reaction between 2,2-diphenylchromene and 1,1-diphenylethylene in acid medium,²³⁰ which has been found to be identical to that obtained from the latter and salicylaldehyde. Protonation of the chromene, ring opening, attack of the olefin by the carbonium ion and ring closure (Scheme 18) lead to the compound (67),



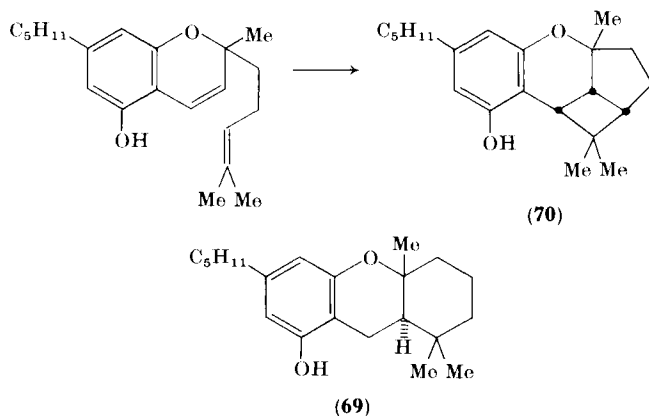
where the chromane ring is formed with the new 1,1-diphenylethylene moiety. Structure and mechanism are supported by deuteration experiments and independent synthesis.²³¹

When the chromene has a side chain with a double bond in a suitable position, acids induce an intramolecular cyclization. Thus for gambogic acid⁷⁴ and cannabichromene^{211,263} the simplest product (**68**) comes from attack of the olefin on the benzylic carbonium ion [Eq. (21)].

²⁶³ B. Yagen and R. Mechoulam, *Tetrahedron Lett.*, 5353 (1969). An additional reduction step, most probably via intermolecular hydride transfer (see above, this section) is necessary to account for the product **69**.



Depending on the acid, the medium, and the particular chromene, other products, such as **69**²⁶³ or the cyclobutane **70**,^{211,263,264} are obtained. Cannabicyclol (**70**) is a natural product, and can also be prepared photochemically (45%)²⁶⁵ by heating in pyridine (1–2%)^{211,266} or with



chloranil.¹⁴³ Its structure, and consequently that of all the similar derivatives of other natural products,²⁶⁷ has been matter of controversy.^{211,266,268} The structure **70**, supported by NMR data,^{211,268} has been confirmed by X-ray analysis of a bromo derivative.²⁶⁹ Whereas the photochemical cyclization is another example of a well-known process, the mechanism of the acid-catalyzed and thermal reaction is still uncertain.²⁷⁰

²⁶⁴ R. K. Razdan and B. A. Zitko, *Tetrahedron Lett.*, 4947 (1969).

²⁶⁵ L. Crombie, R. Ponsford, A. Shani, B. Yagnitinsky, and R. Mechoulam, *Tetrahedron Lett.*, 5771 (1968).

²⁶⁶ V. V. Kane and R. K. Razdan, *Tetrahedron Lett.*, 591 (1969).

²⁶⁷ S. P. Kureel, R. S. Kapil, and S. P. Popli, *Tetrahedron Lett.*, 3857 (1969); *Chem. Ind. (London)*, 958 (1970).

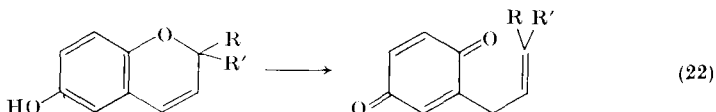
²⁶⁸ V. V. Kane, *Tetrahedron Lett.*, 4101 (1971).

²⁶⁹ M. J. Begley, D. G. Clarke, L. Crombie, and D. A. Whiting, *Chem. Commun.*, 1547 (1970).

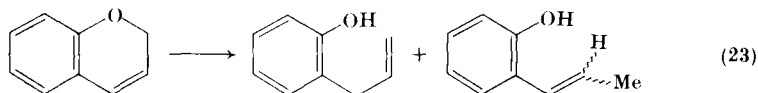
²⁷⁰ A stepwise sequence, involving the formation of a quinonemethide, has been proposed.⁴

C. RING-OPENING REACTIONS

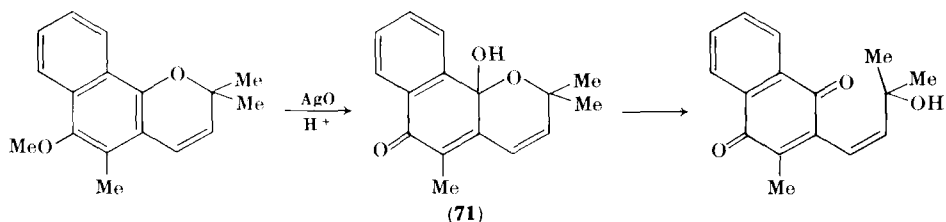
The photochemical ring opening of chromenes to the valence tautomers quinoneallides has been described in Section II. Similar results have been reported recently.¹⁵¹ Another ring opening without change of the oxidation state occurs when 6-hydroxychromenes are treated with bases, such as sodium ethoxide, to give γ,γ -dimethylallylquinones [Eq. (22)]. A mechanism similar to that of the Birch reduction has been



advanced.²⁷¹ With LiAlH_4 or LiAlD_4 there is further reduction, and another mechanism can account for the deuteration results.²⁷² As chromenes behave as aromatic ethers, the cleavage of the C-O bond has been achieved by metal-ammonia,^{191,273,274} Mg in tetrahydrofuran²⁷⁵ or electrochemical reduction [Eq. (23)].²⁷⁶ With some derivatives, the



propenylphenol has been isolated besides the allylphenol.^{275,277} Oxidation of a 6-methoxychromene with AgO and phosphoric acid in dioxan to a surprisingly stable acetal (**71**) was followed by ring opening with bases.²⁷⁸



²⁷¹ H. Morimoto, I. Imada, and G. Goto, *Ann.* **729**, 171 (1969).

²⁷² I. Imada and H. Morimoto, *Chem. Pharm. Bull.* **12**, 1051 (1964); H. Morimoto, I. Imada, M. Watanabe, and H. Sugihara, *Ann.* **715**, 146 (1968).

²⁷³ A. J. Birch and M. Maung, *Tetrahedron Lett.*, 3275 (1967); A. J. Birch, M. Maung, and A. Pelter, *Aust. J. Chem.* **22**, 1923 (1969).

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²⁷⁵ A. Märcker, *J. Organomet. Chem.* **18**, 249 (1969).

²⁷⁶ V. G. Mairanovskii, O. I. Volkova, E. A. Obolnikova, and G. I. Samokhvalov, *Dokl. Akad. Nauk SSSR* **199**, 829 (1971); *Chem. Abstr.* **75**, 136509 (1971).

²⁷⁷ R. K. Razdan, W. R. Thompson, F. E. Granchelli, and H. G. Pars, *Abstr. Int. Symp. Chem. Nat. Prod.*, 7th Riga, 1970 E-113.

²⁷⁸ N. L. Bauld and N. I. Bruckner, *J. Org. Chem.* **36**, 4045 (1971).

VI. Applications

Among chromenes, only the spiropyrans and their heterocyclic derivatives have found a wide practical application as photochromic substances.⁵ 6,7-Chromenediols have been proposed as analytical reagents for the spectrophotometric assay of rare earth cations.²⁷⁹ Chromenes with structure and activity similar to those of hashish constituents have been prepared.²⁸⁰ A number of chromenes, mostly with aryl substituents in positions 2,3, and 4 have been patented as biologically active substances.^{126,280-290}

ACKNOWLEDGMENT

The main part of this review was written during a sabbatical stay at Massachusetts Institute of Technology: the author is indebted to Professor G. Büchi for hospitality and to NATO for financial support.

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- ²⁸⁵ T. Melton and R. W. Tickle, German Pat. 2,050,496 (1971); *Chem. Abstr.* **75**, 35760 (1971).
- ²⁸⁶ R. K. Razdan and W. R. Thompson, German Patent 2,122,643 (1971) [*Chem. Abstr.* **76**, 59455 (1972)]; German Patent 2,135,521 (1972) [*Chem. Abstr.* **76**, 99523 (1972)]; German Patent 2,145,320 (1972) [*Chem. Abstr.* **77**, 5343 (1972)].
- ²⁸⁷ M. Murakami, S. Kawahara, and K. Murase, Japanese Patent 72/00055 (1972); *Chem. Abstr.* **76**, 85697 (1972).
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Tautomerism and Electronic Structure of Biological Pyrimidines*

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I. Introduction*

The understanding of the tautomeric properties of the purine and pyrimidine bases of the nucleic acids and the determination of the electronic properties of the principal tautomers are of fundamental importance in molecular biology, in particular in connection with the theory of mutations (for general references see, e.g. refs. 1-6.) B. Pullman and A. Pullman have presented recently in these *Advances*³ a detailed review of the problem as it concerns the purine bases. The present paper

* Abbreviations used in this chapter: ESR, electron spin resonance; NMR, nuclear magnetic resonance; NQR, nuclear quadrupole resonance; PMR, proton magnetic resonance; CD, circular dichroism; IR, infrared; UV, ultraviolet; MO, molecular orbital; HOMO, highest occupied MO; LUMO, lowest empty MO; HMO, Hückel MO; EHT, extended Hückel theory; IEHT, improved EHT; SCF, self-consistent field; CNDO/2, complete neglect of differential overlap; INDO, intermediate neglect of differential overlap; CI, configuration interaction; STO, Slater-type orbital; AO, atomic orbital; LCAO, linear combination of AO; PCILO, perturbative configuration interaction over localized orbitals; ESCA, electron spectroscopy for chemical analysis; π -SC or ω -technique, self-consistent π -charge; UHF, unrestricted Hartree-Fock.

¹ B. Pullman and A. Pullman, "Quantum Biochemistry." Wiley (Interscience), New York, 1963.

² A. Pullman, in "Electronic Aspects of Biochemistry" (B. Pullman, ed.), p. 135. Academic Press, New York, 1964.

³ B. Pullman and A. Pullman, *Advan. Heterocycl. Chem.* **13**, 77 (1971).

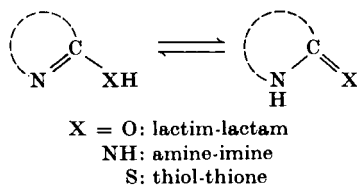
⁴ B. Pullman, in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry" (E. D. Bergmann and B. Pullman, eds.), p. 292. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1970.

⁵ P. O. Löwdin, *Advan. Quant. Chem.* **2**, 213 (1964).

⁶ V. I. Danilov and G. F. Kventzel, "Electronic Representations in the Point Mutation Theory" (in Russian). Naukova Dumka, Kiev, 1971.

is an extension of this review to the pyrimidine bases. The quantum-mechanical methods commonly used in this type of study, having been described in Pullman and Pullman,³ will not be repeated here.

The principal tautomeric properties of the fundamental biological pyrimidines—cytosine, uracil, and thymine—are due to the presence in these N-heteroaromatic compounds of electron-donor substituents such as NH_2 and OH and of SH in some important analogs. The labile hydrogen may remain attached at the exocyclic O, N, or S atom or migrate to one of the ring nitrogens, giving rise to three principal types of tautomerism (Scheme 1):



SCHEME 1

More explicitly, considering the two basic systems cytosine and uracil (thymine is 5-methyluracil and so its tautomerism is essentially analogous to that of uracil), these bases are capable of existing in six (aromatic) tautomeric forms **1–6** and **27–32**, respectively. Nucleosides and nucleotides which are the biological building blocks may exist only in the three forms **2**, **4**, and **6** or **28**, **30**, and **32**, as the result of the replacement of one ring NH of cytosine or uracil, respectively, by ribose or ribose phosphate. The same is true for some of the isomers or analogs of these compounds. The numbering of the heavy atoms adopted throughout this review is indicated in Fig. 1.

Ionization of the pyrimidines (deprotonation or protonation) may occur in different ways resulting in the possibility of a number of tautomeric ionic (anionic and cationic) species. In the case of nucleosides, the number both of tautomeric conversions of the pyrimidines and of their molecular-ionic transformations is, smaller than in the case of the bases themselves.



FIG. 1 Numbering of the heavy atoms.

During recent years a very large amount of work has been carried out, both experimentally and theoretically, in order to elucidate the qualitative and quantitative aspects of pyrimidine tautomerism and to determine the physicochemical properties of the observable tautomeric forms of these molecules. Among the various methods, the determination of the tautomeric form of a molecule by X-ray diffraction technique is the most straightforward. Although the crystallographic parameters describing the positions of hydrogens in the heavy-atom structures are less accurate than those describing the other atoms and, although very often the position of the hydrogens are not directly determined, it is possible to infer these positions from consideration of bond distances and angles of the heavy atoms. For instance, one expects the CO bond length to be of the order of 1.22 Å for a double bond on a ring but near 1.43 Å for a single bond⁷ (the latter value may be rather overestimated as recent X-ray crystallographic studies give the value of 1.33–1.35 Å for the C–O bond lengths in the lactim forms of pyridinols^{8–10}). All the other methods of investigation are based on comparative studies of the physicochemical properties of the molecules and of fixed models of their tautomeric forms (usually methylated derivatives). We present here a review of the experimental and theoretical information pertaining to two aspects of the problem: the evaluation of the nature and extent of pyrimidine tautomerism and the determination of the essential electronic characteristics of the most important tautomers of these bases.

II. Tautomerism of Cytosine

A. THE BASIC SKELETON

Cytosine is generally represented in the lactam-amine form **2** both as a free molecule and in its nucleoside or nucleotide. This is also the form considered to be involved in the base-pairing scheme in DNA.

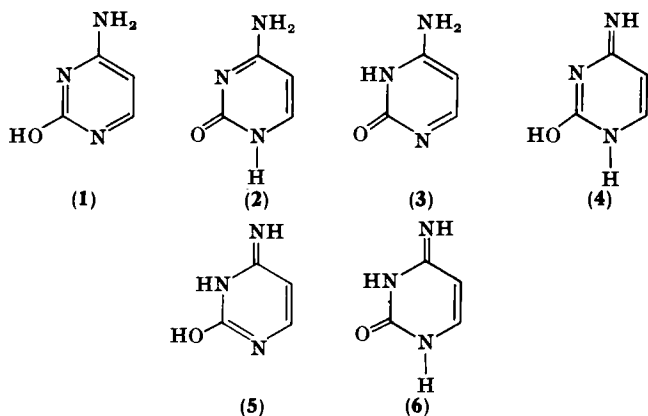
An overwhelming amount of experimental evidence from nearly all the available techniques of physical chemistry seems nowadays to confirm this assignment although the situation was not always clear-cut.

⁷ D. Voet and A. Rich, *Progr. Nucl. Acid Res. Mol. Biol.* **10**, 183 (1970).

⁸ Å. Kvik and I. Olovsson, *Ark. Kemi* **30**, 71 (1968).

⁹ J. Almlöf, Å. Kvik, and I. Olovsson, *Acta Crystallogr. Sect. B* **27**, 1201 (1971).

¹⁰ L. H. Voight and J. G. Wirth, *J. Amer. Chem. Soc.* **93**, 5402 (1971).



X-ray crystal results on cytosine itself^{10a-13} (anhydrous and monohydrate), its complexes with different partners,¹⁵⁻²⁰ cytidine,²¹ and cytidine 2',3'-cyclic phosphate²² all indicate its existence in the lactam-amine form (2). In a number of crystals the cytosine ring is protonated, invariably at N-3.²³⁻³² In cytosine 5-acetic acid³³ half of the molecules

^{10a} Jeffrey and Kinoshita¹² have used a different numbering of the ring atoms of cytosine from that of Barker and Marsh,¹¹ the latter being the same as the numbering used here. A superficial reading of the papers may lead to the erroneous conclusion¹⁴ that cytosine in the crystals take on different tautomeric forms depending upon the solvent used for recrystallization.

- ¹ D. L. Barker and R. E. Marsh, *Acta Crystallogr.* **17**, 1581 (1964).
- ¹² G. A. Jeffrey and Y. Kinoshita, *Acta Crystallogr.* **16**, 20 (1963).
- ¹³ R. J. McClure and B. M. Craven, *Acta Crystallogr. Sect. B* **29**, 1234 (1973).
- ¹⁴ D. L. Breen and R. L. Flurry, *Theor. Chim. Acta* **23**, 138 (1971).
- ¹⁵ A. E. V. Haschemeyer and H. M. Sobell, *Acta Crystallogr.* **19**, 125 (1965).
- ¹⁶ E. J. O'Brien, *J. Mol. Biol.* **22**, 377 (1966).
- ¹⁷ E. J. O'Brien, *Acta Crystallogr.* **23**, 92 (1967).
- ¹⁸ D. Voet and A. Rich, *J. Amer. Chem. Soc.* **91**, 3069 (1969).
- ¹⁹ S. H. Kim and A. Rich, *J. Mol. Biol.* **42**, 87 (1969).
- ²⁰ M. Sundaralingam and J. A. Carrabine, *J. Mol. Biol.* **61**, 287 (1971).
- ²¹ S. Furberg, C. S. Peterson, and C. Rømming, *Acta Crystallogr.* **18**, 313 (1965).
- ²² C. L. Coulter, *J. Amer. Chem. Soc.* **95**, 670 (1973).
- ²³ E. Alver and S. Furberg, *Acta Chem. Scand.* **13**, 910 (1959).
- ²⁴ R. F. Bryan and K. Tomita, *Nature (London)* **192**, 812 (1961).
- ²⁵ R. F. Bryan and K. Tomita, *Acta Crystallogr.* **15**, 1174 (1962).
- ²⁶ M. Sundaralingam and L. H. Jensen, *J. Mol. Biol.* **13**, 914 (1965).
- ²⁷ M. Sundaralingam and L. H. Jensen, *J. Mol. Biol.* **13**, 930 (1965).
- ²⁸ C. E. Bugg and R. E. Marsh, *J. Mol. Biol.* **25**, 67 (1967).
- ²⁹ E. Subramanian and H. K. Hunt, *Acta Crystallogr. Sect. B* **26**, 303 (1970).
- ³⁰ B. L. Trus and R. Marsh, *Acta Crystallogr. Sect. B* **28**, 1834 (1972).
- ³¹ C. Tamura, T. Hata, S. Sato, and N. Sakurai, *Bull. Chem. Soc. Jap.* **45**, 3254 (1972).
- ³² J. S. Shersfinski and R. E. Marsh, *Acta Crystallogr. Sect. B* **29**, 192 (1973).
- ³³ R. E. Marsh, R. Bierstedt, and E. L. Eichhorn, *Acta Crystallogr.* **15**, 310 (1962).

are randomly protonated at N-3 and the same system of half-protonated cytosine residues is found in the crystalline state of the helical polyribocytidylic acid,³⁴ whose structure in solution moreover seems similar to that in the solid state.^{35,36}

Early *infrared (IR) spectroscopy* studies were inconclusive; some^{37,38} were considered to indicate that cytosine exists in the amine-lactim form (**1**) in the solid state, others³⁹⁻⁴¹ that it exists in the amine-lactam form (**2** or **3**). More recent studies⁴²⁻⁵⁰ (for reviews, see refs. 51, 52) on cytidine, 5-halodeoxycytidines, sodium cytidylate, and polycytidylic acid in neutral H₂O or D₂O solution advocate, however, the structure **2** for the cytosine residue.

Differences in the IR spectra of cytosine, cytidine, and cytidylic acid were considered by Angell.⁴¹ This author concluded that the cytidylic acids exist in the solid state in a zwitterion form with one of the hydrogen atoms from the phosphate group at N-3 of the cytosine ring (cf. refs.^{53,54}). Previously Miles⁴⁴ postulated that the form **7a** rather than the form **8** was the structure of cytidine in acid solution. This conclusion is essentially the same as that of Tsuboi *et al.*⁴⁷ who proposed form **7b** for the protonated form of cytidine, as **7a** and **7b** are two canonical forms of the same tautomer (**7**).

³⁴ R. Langridge and A. Rich, *Nature (London)* **198**, 725 (1963).

³⁵ E. O. Akinrimisi, C. Sander, and P. O. P. Ts'o, *Biochemistry* **2**, 340 (1963).

³⁶ K. A. Hartmann, and A. Rich, *J. Amer. Chem. Soc.* **87**, 2033 (1965).

³⁷ E. R. Blout and M. Fields, *J. Amer. Chem. Soc.* **72**, 479 (1950).

³⁸ M. M. Stimson and M. J. O'Donnell, *J. Amer. Chem. Soc.* **74**, 1805 (1952).

³⁹ H. W. Thompson, D. L. Nicholson, and L. N. Short, *Discuss. Faraday Soc.* **9**, 222 (1950).

⁴⁰ L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).

⁴¹ C. L. Angell, *J. Chem. Soc.*, 504 (1961).

⁴² H. T. Miles, *Biochim. Biophys. Acta* **22**, 247 (1956).

⁴³ E. M. Tanner, *Spectrochim. Acta* **8**, 9 (1956).

⁴⁴ H. T. Miles, *Biochim. Biophys. Acta* **27**, 46 (1958).

⁴⁵ H. T. Miles, *Biochim. Biophys. Acta* **35**, 274 (1959).

⁴⁶ H. T. Miles, *Proc. Nat. Acad. Sci. U.S.A.* **47**, 791 (1961).

⁴⁷ M. Tsuboi, Y. Kyogoku, and T. Shimanouchi, *Biochim. Biophys. Acta* **55**, 1 (1962).

⁴⁸ H. T. Miles, *J. Amer. Chem. Soc.* **85**, 1007 (1963).

⁴⁹ T. L. V. Ulbricht, *Tetrahedron Lett.* **16**, 1027 (1963).

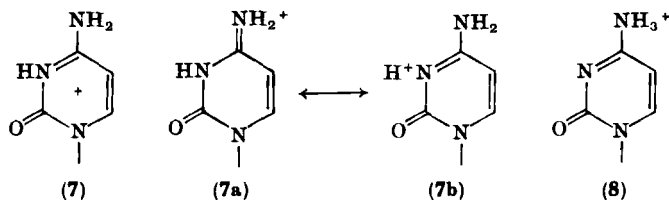
⁵⁰ H. Fritzsche and M. Hartmann, *Z. Chem.* **11**, 69 (1971).

⁵¹ T. Shimanouchi, M. Tsuboi, and Y. Kyogoku, *Advan. Chem. Phys.* **7**, 435 (1964).

⁵² I. Tinoco, and D. N. Holcomb, *Annu. Rev. Phys. Chem.* **15**, 371 (1964).

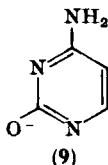
⁵³ E. R. Blout and M. Fields, *J. Biol. Chem.* **178**, 335 (1949).

⁵⁴ R. J. C. Harris, S. F. D. Orr, E. M. F. Roe, and J. F. Thomas, *J. Chem. Soc.*, 489 (1953).



In general, the problem of tautomerism in nucleic acid bases has been approached by comparing the IR spectra of several isoelectronic model compounds. The model corresponding to the cytosine tautomers 4 or 5 have not yet been investigated. The IR spectroscopy studies cannot therefore definitely rule out these tautomers. It seems, however, that they do rule out form 6 for cytosine and cytidine and indicate that the dominant tautomer of the compounds in aqueous solution is the lactam-amino form 2, and that the protonated cations have the structure 7.

The conclusions from IR spectroscopy have been confirmed by recent *Raman spectroscopy* studies^{55,56} on the constituent bases of RNA, their nucleosides and nucleotides, and on related model compounds. The Raman spectra of cytosines rule out the prevalence of the imine form 6 in solution and indicate that the neutral molecules have the structure 2. They also indicate that the removal of a proton from the free base leads to an anion of type 9, and that in the cation N-3 is the site of protonation.



The pyrimidine bases, their derivatives, nucleotides, and nucleosides have been extensively studied by *NMR techniques* including proton magnetic resonance (PMR), carbon-13, nitrogen-15, and fluorine-19 magnetic resonances as well as nitrogen-14 *nuclear quadrupole resonance* (¹⁴N NQR).

The first PMR spectra^{57,58} attributed the tautomeric structure (7) to the cation of cytosine, in agreement with X-ray studies and IR data. For the preferred neutral form of cytosine in solution Kokko *et al.*⁵⁹

⁵⁵ R. C. Lord and G. J. Thomas, *Spectrochim. Acta, Part A* **23**, 2551 (1967).

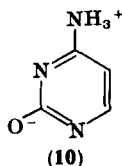
⁵⁶ R. C. Lord and G. J. Thomas, *Develop. Appl. Spectrosc.* **6**, 179 (1968).

⁵⁷ C. D. Jardetzky and O. Jardetzky, *Federation Proc.* **17**, 380 (1958).

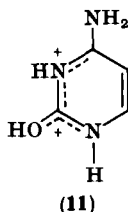
⁵⁸ C. D. Jardetzky and O. Jardetzky, *J. Amer. Chem. Soc.* **82**, 222 (1960).

⁵⁹ J. P. Kokko, J. H. Goldstein, and L. Mandell, *J. Amer. Chem. Soc.* **83**, 2909 (1961).

originally suggested the zwitterionic form **10** in deuterated dimethyl sulfoxide and claimed that the same structure existed in water (for



cytosine cation they suggested the form **8**). Later, however, Katritzky and Waring⁶⁰ showed that the predominant tautomer of cytosine in dimethyl sulfoxide and in aqueous solution has structure **2**, and that cytosine undergoes protonation at N-3. The same form for the predominating tautomer of cytosine, its N-1 and N-alkylamino derivatives and of cytidines, as well as the addition of the proton at the 3-position of these compounds, was confirmed by other PMR studies.⁶¹⁻⁶⁶ The assignment of the N-3 position of the cytosine residue as the site of protonation is consistent with the recent NMR evidence that in the zinc complexes of cytidine the cytosine ring is bound to zinc through N-3^{67,68} (cf. review⁶⁹ on sites of proton ionization and sites of metal ion coordination of DNA, RNA, and their constituents). A recent PMR study⁶⁵ demonstrates that double protonation of cytosine in FSO₃H or FSO₃H-SbF₅-SO₂ solution yields the structure **11**.



Gatlin and Davis⁶¹ proposed that whereas cytidine existed in the amine form **2**, 2'-deoxycytidine was the imine **6**. This interpretation however, is incorrect^{48,49,63} because they did not measure cytidine or

⁶⁰ A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963).

⁶¹ L. Gatlin and J. C. Davis, *J. Amer. Chem. Soc.* **84**, 4464 (1962).

⁶² H. T. Miles, R. B. Bradley and E. D. Becker, *Science* **142**, 1569 (1963).

⁶³ O. Jardetzky, P. Pappas, and N. G. Warde, *J. Amer. Chem. Soc.* **85**, 1657 (1963).

⁶⁴ R. R. Shoup, H. T. Miles, and E. D. Becker, *J. Amer. Chem. Soc.* **89**, 6200 (1967).

⁶⁵ R. Wagner and W. Von Philipsborn, *Helv. Chim. Acta* **53**, 299 (1970).

⁶⁶ W. Hutzenlaub and W. Pfeiderer, *Chem. Ber.* **106**, 665 (1973).

⁶⁷ S. M. Wang and N. C. Li, *J. Amer. Chem. Soc.* **90**, 5069 (1968).

⁶⁸ K. C. Tewari, J. Lee, and N. C. Li, *Trans. Faraday Soc.* **66**, 2069 (1970).

⁶⁹ R. M. Izatt, J. J. Christensen, and J. H. Rytting, *Chem. Rev.* **71**, 439 (1971).

deoxycytidine, but only their salts—cytidine hemisulfate and deoxycytidine hydrochloride. In fact, the two free bases are in the amine form **2**, and the difference, between the PMR spectra of free deoxycytidine and its hydrochloride is attributed^{48,49} to protonation of the cytosine ring in the acid salt, the result being consistent with IR data.

The results of the above studies indicate that proportions of the other tautomeric forms, for instance the imine **6**, are very small under ordinary conditions. Very recently new PMR studies⁷⁰⁻⁷⁴ on cytosine, guanine, and their derivatives claimed to show that much higher fractions of the rare tautomers of cytosine and guanine were present at room temperatures in neutral aqueous solution. The unusually broad resonances of the cytosine-H-5 protons in the PMR spectra were examined as a function of temperature, concentration, and solution pD, as well as of the external magnetic field. The authors⁷¹⁻⁷⁴ considered that the line broadening arose from chemical exchange between the amine and imine tautomers of cytosine, and from a detailed kinetic analysis of the problem they concluded that the imine tautomer of cytosine was present in the amount of $15 \pm 3\%$ at room temperature in neutral aqueous solution. Such a result if true would have significant importance for the theory of mutation in genetic replication (abnormal adenine-cytosine base pairings). These findings, however, have been shown to be erroneous, being due to contamination by paramagnetic ions, a common source of line broadening.⁷⁵ Thus Wong *et al.*^{76,77} presented evidence that the unusual broadening of the cytosine-H-5 protons was not reproducible with purified samples of cytidine 5'-monophosphate. The broadening appeared with addition of paramagnetic impurities (Cu^{2+}). This fact has since been acknowledged by the original authors⁷⁸.

⁷⁰ B. W. Bangerter and S. I. Chan, *J. Amer. Chem. Soc.* **91**, 3910 (1969).

⁷¹ G. C. Y. Lee, J. H. Prestegard, and S. I. Chan, *Biochem. Biophys. Res. Commun.* **43**, 435 (1971).

⁷² S. I. Chan and G. C. Y. Lee, in "The Purines—Theory and Experiment" (E. D. Bergmann and B. Pullman, eds.), p. 277. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1972.

⁷³ G. C. Y. Lee, J. H. Prestegard, and S. I. Chan, *J. Amer. Chem. Soc.* **94**, 951 (1972).

⁷⁴ G. C. Y. Lee and S. I. Chan, *J. Amer. Chem. Soc.* **94**, 3218 (1972).

⁷⁵ A. Abragam, "The Principles of Nuclear Magnetism." Oxford Univ. Press, London and New York, 1962.

⁷⁶ Y. P. Wong, K. L. Wong, and D. R. Kearns, *Biochem. Biophys. Res. Commun.* **49**, 1580 (1972).

⁷⁷ Y. P. Wong, *J. Amer. Chem. Soc.* **95**, 3511 (1973).

⁷⁸ M. Pieber, P. A. Kroon, J. H. Prestegard, and S. I. Chan, *J. Amer. Chem. Soc.* **95**, 3408 (1973).

Carbon-13 magnetic resonance spectra of the naturally occurring cytidines have been described in several papers.⁷⁹⁻⁸² The electronic structure of the compounds is reflected in the carbon-13 shifts. For instance, the observed chemical shifts for these and other pyrimidine and purine nucleosides were correlated, at least qualitatively, with the calculated charge densities (see Section VIII) and with the known reactivity of these molecules. It is difficult to draw conclusions from the carbon-13 spectra about the tautomerism of cytosine.

NMR information on the electronic environment of the nitrogen and oxygen atoms in nucleic acid bases is of particular interest in view of the importance of base pairing. Only NMR spectra of nitrogen seem to have been reported. Early empirical correlations between the hybridization of nitrogen and the nitrogen-15 chemical shifts⁸³ and coupling constants⁸⁴ were expected to help in the identification of the tautomeric forms and of sites of protonation. The initial work dealt with 1-methylcytosine,^{62,85} and led to an unambiguous proof that the predominant tautomeric form of 1-methylcytosine as well as of cytosine nucleosides was the amino form **2** and that in acid the ring was protonated at N-3. The results of related NMR studies^{64,86-90} on restricted rotation of the amino group, and the protonation, of several cytosines have been similarly interpreted. Some aspects of these studies will be discussed later (Section III).

Further support for structure **2** as the dominant tautomer of cytosine came from the analysis of the ¹⁴N NQR spectra of cytosine, cytidine,

⁷⁹ A. J. Jones, M. W. Winkley, D. M. Grant, and R. K. Robins, *Proc. Nat. Acad. Sci. U.S.* **65**, 27 (1970).

⁸⁰ A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Amer. Chem. Soc.* **92**, 4079 (1970).

⁸¹ A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Phys. Chem.* **74**, 2684 (1970).

⁸² D. E. Dorman and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.* **65**, 19 (1970).

⁸³ J. B. Lambert, G. Binsch, and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.* **51**, 735 (1964).

⁸⁴ G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.* **86**, 5564 (1964).

⁸⁵ B. W. Roberts, J. B. Lambert, and J. D. Roberts, *J. Amer. Chem. Soc.* **87**, 5439 (1965).

⁸⁶ E. D. Becker, H. T. Miles, and R. B. Bradley, *J. Amer. Chem. Soc.* **87**, 5575 (1965).

⁸⁷ I. Adams, G. P. Jones, and J. M. Thomas, *Trans. Faraday Soc.* **66**, 1854 (1970).

⁸⁸ R. R. Shoup, E. D. Becker, and H. T. Miles, *Biochem. Biophys. Res. Commun.* **43**, 1350 (1971).

⁸⁹ R. R. Shoup, H. T. Miles, and E. D. Becker, *J. Phys. Chem.* **76**, 64 (1972).

⁹⁰ R. R. Shoup, E. D. Becker, and M. L. McNeel, *J. Phys. Chem.* **76**, 71 (1972).

and some model compounds.^{91,92} The tautomeric form found for the cytosine ring was invariably the lactam-amine.

The *ionization constants* of cytosine, cytidine, and their derivatives have been determined by spectrophotometry and by titration, at first without ascertaining their dependence on ionic strength or temperature, but later with the ionization constants determined over the range of 10–50°, and the thermodynamic enthalpy and entropy changes for proton ionization evaluated.^{93–95} An assumption is commonly used for structural analysis of organic compounds that the blocking of a proton-acceptor center of a molecule, for example by a methyl group, does not significantly change the acid-base properties of the other acceptor-centers. Starting from the comparative study of the ionization constants of cytosine and of its several methylated derivatives (representing fixed models of tautomeric forms), it is evident (see Table I) that cytosine and cytidine exist in aqueous solution mainly in form **2** (cf. refs. 60, 96). It is true that no *pK* value is known for the methylated cytosine corresponding to the form **5**, but the *pK* of the lactim-imine form **5** should certainly be considerably higher than that of the lactam-amine form **2**.

From the comparison of ionization constants it was also deduced that both 1-methyl and 3-methyl cytosines exist predominantly in the lactam-amine forms **2** and **3**, respectively.^{100,102} The conclusions based on a comparison of ionization constants have been confirmed by UV analysis (see below).

The tautomeric ratios characterizing the complex scheme of tautomeric conversions of cytosine have not been evaluated. The only quantitative results concern the relative contributions of structures **2**,

⁹¹ D. T. Edmonds and P. A. Speight, *J. Magn. Reson.* **6**, 265 (1972).

⁹² R. Blinc, M. Mali, R. Osredkar, A. Prelesnik, J. Seliger, I. Zupančič, and L. Ehrenberg, *J. Chem. Phys.* **57**, 5087 (1972).

⁹³ S. Lewin and D. A. Humphreys, *J. Chem. Soc. B*, 210 (1966).

⁹⁴ J. J. Christensen, J. H. Rytting, and R. M. Izatt, *J. Phys. Chem.* **71**, 2700 (1967).

⁹⁵ J. J. Christensen, J. H. Rytting, and R. M. Izatt, *J. Chem. Soc. B*, 1643 (1970).

⁹⁶ D. J. Brown and J. M. Lyall, *Aust. J. Chem.* **15**, 851 (1962).

⁹⁷ A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962).

⁹⁸ J. J. Fox and D. Shugar, *Biochim. Biophys. Acta.* **9**, 369 (1962).

⁹⁹ B. I. Sukhorukov, A. S. Gukovskaya, L. N. Sukhoruchkina, and G. I. Lavrenova, *Biofizika* **17**, 5 (1972).

¹⁰⁰ G. W. Kenner, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 855 (1955).

¹⁰¹ I. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.* **83**, 4755 (1961).

¹⁰² T. Ueda and J. J. Fox, *J. Amer. Chem. Soc.* **85**, 4024 (1963).

TABLE I
COMPARISON OF THE pK VALUES FOR THE FIRST IONIZATION OF CYTOSINES AND CYTIDINES

Type of tautomer	Compound	Ref:	98	99	96	pK values ^a					103
						100	94	101	60	102	
1	2-Methoxycytosine		5.3	5.41 ^b							
	2-Methoxy- N^8 , N^8 -dimethylcytosine			$\lesssim 6.17$							
2	Cytosine ^c		4.45	4.60 ^b		4.57	4.58 ^d	4.61 ^e			
	1-Methylcytosine		4.55	4.61 ^b							
	Cytidine ^c		4.1				4.08 ^d				
	N^8 , N^8 -Dimethylcytosine							4.25 ^e			
	1-Methyl- N^8 , N^8 -dimethylcytosine					4.20					
	1-Methyl- N^8 -methylcytosine			4.38 ^b		4.47					
3	3-Methylcytosine			7.49 ^b					7.49 ^f	7.4	7.38
4	1-Methyl-2-methoxycytosine			~ 12.0							
6	1,3-Dimethylcytosine		9.33 ^b			9.29					9.4
	3-Methylcytidine									8.73	8.7
	1,3-Dimethyl- N^8 -methylcytosine		9.65 ^b								

^a Determined spectrophotometrically unless otherwise indicated.

^b At 20°C; the accuracy of determination of pK values was ± 0.66 .

^c For the collection of pK values determined at various ionic strengths and temperatures, see Refs. 93 and 95.

^d Potentiometrically determined values at 25°C; the accuracy of determination of pK was ± 0.01 .

^e The accuracy of determination of pK was ± 0.05 .

^f At 20°C; titrated in 0.017 M solution.

3, and 6 of cytosine in the molecular ground state as well as in the excited state. Since experimental evidence shows that cytosine, 1- and 3-methylcytosines, and 1,3-dimethylcytosine are protonated to give cations of similar structure, it was possible to evaluate the tautomeric ratios $K_t^{2,3} = 2/3$ (population of form 2/population of form 3) and $K_t^{2,6} = 2/6$. Tautomeric ratios determined indicate that in aqueous solution tautomer 2 predominates over tautomers 3 or 6 by factors of about of 10^3 or $10^{4.6}$, respectively (see Table II). Similarly, the lactam-amine form 2 of cytidine prevails over its lactam-imine tautomer 6 with a factor of $\sim 10^5$.

Sukhorukov *et al.*⁹⁹ measured the displacement of the near ultra-violet absorption bands of several cytosines upon transition from the neutral to the ionic form and evaluated the ionization constants in the excited state of the compounds. They concluded that on excitation there was no considerable shift in the tautomeric equilibrium of the forms 2 and 6 [$(K_t^{2,6}$ (in the excited state) = 1.55×10^4]. They also attempted to evaluate the concentration of several molecular and

TABLE II
TAUTOMERIC CONSTANTS AND THERMODYNAMIC PARAMETERS
FOR CYTOSINE TAUTOMERS

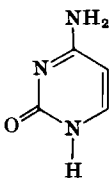
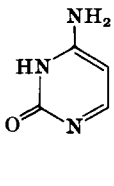
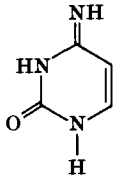
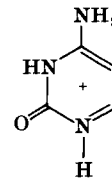
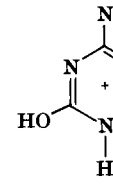
Experimental tautomeric ratios			Method	References
$K_t^{2,3}$	$K_t^{2,3}$	$K_t^{2,6}$		
$10^{2.9}$	60	$6 \times 10^{3.9}$	p <i>K</i> measurement in aqueous solution	97
	100	$10^{4.9}$		99 ^a
0.84×10^3	62.8	5.26×10^4	UV spectra measurements ^b (at 30°, 50°, and 70°, respectively)	104
		3.3×10		
		1.8×10		
		0.8×10		
Thermodynamic parameters for conversion 2 → 6				
Energy difference $\Delta E \approx 5.5$ kcal/mole			From temperature dependence of the K_t values	104
Entropy difference $\Delta S^\circ \approx -12$ cal/mole .deg.				
Free-energy difference $\Delta F \approx 6.73$ kcal/mole			UV spectroscopy	99
Heat of tautomeric transition $\Delta H_t \approx 5.72$ kcal/mole				

^a Calculated using pK = 7.4 for 3-methylcytosine.^{102,103,105}

^b Uncertain evaluation (see text).

TABLE III

CONCENTRATION OF MOLECULAR AND PROTONATED FORMS^a OF CYTOSINE
(*t* = 20°, AQUEOUS SOLUTION) EVALUATED FROM IONIZATION CONSTANTS⁹⁹

					
	(2)	(3)	(6)	(7)	(7)
Ground state	99.862	0.136	0.002	99.842	0.158
Excited state	99.993	—	0.007	—	—

^a On the basis of the influence of the methyl group on the *pK* values of several derivatives of cytosine, it was postulated⁹⁹ that the main proton-acceptor center for 2-methoxycytosine was apparently N-1. A similar conclusion was postulated¹⁰² on the basis of methylation studies of 2-methoxycytosine in which the 1-methiodide rather than the N-3 derivative was obtained.

protonated forms in the ground as well as in the excited state of cytosine.⁹⁹ It may be seen from Table III that the concentration of the lactam-imine form 6 both in the ground and in the excited state is small and that the dominant tautomer of protonated cytosine has hydrogen atoms at positions N-1, N-3, and N-8. However, the contributions of the other forms have not been taken into account. The figures quoted in Table III cannot thus be treated as definite values of the tautomeric concentrations.

On the basis of the temperature dependence of the *pK* values, it was postulated⁹⁹ that with rise in temperature the relative amount of form 2 diminishes, while those of forms 3 and 6 increase. An attempt has also been made to evaluate both the free energy change and the heat of the tautomeric conversion from form 2 to form 6. These values were estimated as 6.73 and 5.72 kcal/mole, respectively.

The near *UV absorption spectra* of cytosine, cytidine, and their derivatives have been measured in different solutions and in the solid state. Early works by Stimpson and O'Donnell⁹⁸ were thought to confirm the previous conclusion from IR evidence that cytosine exists in the lactim-amine form 1. However, all later UV studies indicate that the predominating form both of cytosine and cytidine is lactam-amine

¹⁰³ P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).

¹⁰⁴ H. Morita and S. Nagakura, *Theor. Chim. Acta* **11**, 279 (1968).

¹⁰⁵ I. Wempen and J. J. Fox, *J. Amer. Chem. Soc.* **86**, 2474 (1964).

2. For instance Shugar and Fox¹⁰⁶ have shown that the spectrum of cytosine resembles that of 1-methylcytosine (form 2), not that of 2-methoxycytosine (form 1). Similarly, Kenner *et al.*¹⁰⁰ have established that lactam-imine forms 6 were unimportant both for 1-methylcytosine (thus also for cytosine itself) and for its aminoacetyl derivatives. Katritzky and Waring⁶⁰ have extended these studies and in particular showed that tautomers 3 and zwitterionic structures 10 were unimportant in the tautomeric equilibrium in both aqueous and dimethyl sulfoxide solutions. Although these last comparisons were made with only two partially methylated cytosines still capable of tautomerism, the reported conclusions agree with those reached later by Brown and Lyall⁹⁶ on much wider evidence.

As far as we are aware, the absorption spectrum of a model compound corresponding to the tautomer 5 of cytosine has not been measured, so it is difficult to eliminate the possibility of the existence of cytosine in form 5 on the basis of the UV spectra alone. This is ruled out, however, on *pK* considerations.⁹⁶

It is interesting that the dominant form of 3-methylcytosine in aqueous solution has been established¹⁰² as form 3 rather than the imine forms 5 or 6. This conclusion agrees with that drawn from *pK* analysis (cf. the *K_t* values in Table III) that the concentration of tautomers 6 is smaller than that of tautomers 3.

As to cytidine, it also is shown to exist mainly in form 2 (cf. e.g. ref. 107).

The UV also provides a means of prediction of the anionic and cationic forms of cytosine and cytidine. It is known that there are no great differences between the spectra of amino-substituted aromatic hydrocarbons and the corresponding anions of molecules in which an amino group is replaced by a hydroxy group. The absorption bands of the anions are slightly shifted toward longer wavelengths and their intensities are somewhat stronger compared to those of the amino compounds. This analogy between the spectra of phenoxides and the corresponding amines is known as the Jones rule.

This situation is different in the case of anionic forms of polyhydroxy N-heterocycles or systems with one hydroxy group and other easily ionized acidic substituents (e.g., mercapto groups) because the negative charge is here distributed between the ring nitrogens and oxygen (or sulfur). However, in the cases of simple compounds with one hydroxy group (e.g., monoxoazines or their amino, methoxy, or methylmercapto

¹⁰⁶ D. Shugar and J. J. Fox, *Biochim. Biophys. Acta* **9**, 199 (1952).

¹⁰⁷ W. C. Johnson, P. M. Vipond and J. C. Girod, *Biopolymers* **10**, 923 (1971).

derivatives), the opinion prevails that the anions conserve essentially their negative charge at the oxygen atom. Accordingly, one expects the analogies between the UV spectra of anionic forms of these hydroxy compounds and of the corresponding amino derivatives to be similar to those of aromatic hydrocarbons. Under these conditions, it is possible to correlate the spectrum of the cytosine anion with the spectra of 2-methoxycytosine and 2,4-diaminopyrimidine (Table IV).

As to the cationic structures of cytosine, the UV evidence^{60,102,108} shows that the cations of cytosine itself and of its 1- and 3-methyl derivatives all have structures of type 7.

The UV spectra also give clear evidence that protonation of cytosine does not occur at the amino group. There are appreciable differences between the spectra of amino compounds and the parent unsubstituted molecules. The spectra of the amines however, become closely similar to those of the unsubstituted molecules on cation formation at the

TABLE IV

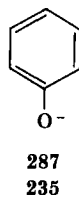
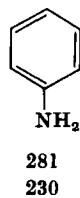
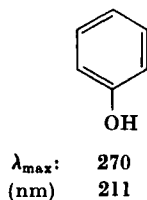
ANALOGIES BETWEEN THE SPECTRA OF MOLECULES WITH OH, NH₂, AND O⁻ SUBSTITUENTS

Bathochromic effect of substituents:

In aromatic hydrocarbons:

OH(OMe) < NH₂ < O⁻

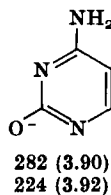
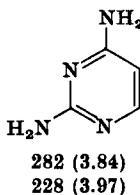
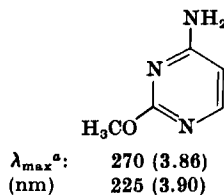
e.g.



In N-heteroaromatic molecules:

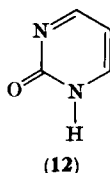
OMe < NH₂ ≈ O⁻
OMe < O⁻ < NH₂

e.g.,



^a The values of log ϵ are given in parentheses.

amino group (NH_3^+) (see e.g. ref. 109). With a proton at the amino group [form 7], the cytosine cation should have a spectrum resembling that of neutral 2-pyrimidone (12). This is not the case.⁶⁰ It is worth noting that



no monofunctional attack at the amino group of cytidine has been found in the chelates of cytidine.¹¹⁰

Similar considerations were used^{60,96} to rule out the zwitterionic structure of cytosine as its main form in aqueous solution. As a zwitterion (10) cytosine ought to have a spectrum similar to that of the anion of 2-oxopyrimidine. The differences between the spectra of the two compounds indicate that this is not the case.

UV spectroscopy is a sensitive tool for the elucidation of structures of molecules only if the different tautomers have distinct spectra. In some cases, cytosine or cytidine and their alkylated analogs have similar spectra with seriously overlapping bands, and thus the application of UV spectroscopy to the elucidation of the tautomeric structures of the molecules is inconclusive. In particular, the method is unreliable for the determination of tautomeric equilibria of cytosine (see below). Nevertheless the UV absorption spectra confirm the conclusions drawn from other studies as to the main form of cytosine and cytidine in aqueous solution at room temperature.

It has been observed,^{104,107,111-115} however, that some of these compounds undergo a large change in their electronic absorption spectra on going from aqueous to nonaqueous solution. Similar changes of the spectra have also been found upon heating aqueous solutions of these compounds.^{104,111,112} These spectral changes have been the

¹⁰⁹ "UV Atlas of Organic Compounds." Butterworth, London, and Verlag Chemie, Weinheim.

¹¹⁰ S. Mansy, B. Rosenberg, and A. J. Thomson, *J. Amer. Chem. Soc.* **95**, 1633 (1973).

¹¹¹ C. Hélène, A. Haug, M. Delbrück, and P. Douzou, *C.R. Acad. Sci.* **259**, 3385 (1964).

¹¹² C. Hélène, and P. Douzou, *C.R. Acad. Sci.* **259**, 4853 (1964).

¹¹³ C. Hélène, Ph. D. Thesis, Univ. Paris, 1966.

¹¹⁴ E. Charney and M. Gellert, *Biopolym. Symp.* **1**, 469 (1964).

¹¹⁵ K. Berens and K. L. Wierzchowski, unpublished data.

subject of controversy. Some authors have concluded that this behavior was connected with the change of tautomeric ratios between several tautomers caused by the nature of solvent and the temperature. Hélène *et al.*¹¹¹⁻¹¹³ advanced the hypothesis that (i) in an aqueous solution the dominant tautomer of cytosine, its 1-methyl derivative, and cytidine, is of type **2** and that tautomers **4** and **6** exist in small amounts, and (ii) the concentration of these last two tautomers increases with rise in temperature or with the change of solvent (for instance, from an aqueous solution to alcoholic). The spectral study of photoproducts of the compound^{111,113} was stated to confirm this conclusion. But no evaluation of the tautomeric ratio has been made because of overlapping of the absorption bands of several tautomers.

However Morita and Nagakura¹⁰⁴ concluded from similar studies that in aqueous solution cytosine exists as an equilibrium mixture of two forms, **2** and **6**, only. According to these authors the first form predominates in trimethyl phosphate and water at room temperature, but the second prevails at high temperature. The imine form is considered to predominate also in acetonitrile. From the temperature dependence of the absorption spectrum of cytosine in aqueous solution, Morita and Nagakura estimated the tautomeric ratios $K_1^{2,6}$ to be equal to 33, 14, and 8 at 30, 50, and 70°, respectively. The energy^{115a} and entropy differences between the imine form **6** and the amine form **2** were evaluated as ~5.5 kcal/mole and ~12 cal/mole. deg., respectively.

The evidence of Morita and Nagakura was the first experimental indication of a relatively large amount (~3%) of the imine tautomer **6** of cytosine near room temperature in aqueous solution. Other workers have, however, proposed that the observed differences in the UV spectra of cytosine or cytidine with change in medium could be attributed to the existence of hydrogen-bonded solvent-solute complexes.^{107,115} In a paper quoted earlier,¹⁰⁷ the spectra of cytidine, 3-methyl-, and *N,N*-dimethylcytidine have been measured not only in aqueous solution but also in several other solvents differing in polarizability and dielectric constant. The observed spectral changes of cytidines showed that the imine tautomer of cytidine could not exist to an appreciable extent even in organic solvents. The differences between the spectra of cytidine in various solvents were attributed to hydrogen bonding and the equilibrium between the species found upon heating the aqueous solution of cytosine or cytidine was postulated to be a measure of the stability of the hydrogen-bonded complex.

^{115a} Morita and Nagakura¹⁰⁴ have used the symbol ΔH° , usually denoting the enthalpy difference, for the difference in energy between two tautomers. This misleading notation led to the erroneous conclusion¹⁰⁷ that the difference in free energy between two tautomers has been measured to be 2 kcal/mole.

For comparison with the theoretical predictions, we have collected in Table II, together with the previously discussed tautomeric constants, some thermodynamic parameters characterizing the tautomeric conversion of cytosine.

B. SUBSTITUENT EFFECTS ON TAUTOMERIC EQUILIBRIA OF CYTOSINE

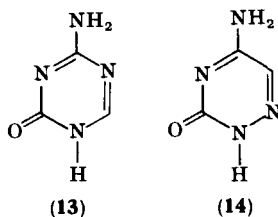
The shifts of the tautomeric equilibria (lactam \rightarrow lactim, amine \rightarrow imine, or thione \rightarrow thiol) in N-heterocyclic molecules caused by substituents are of considerable interest. Several such studies are available for cytosines.

1. Halogen Substitution: Tautomeric Shift 2 \rightarrow 3

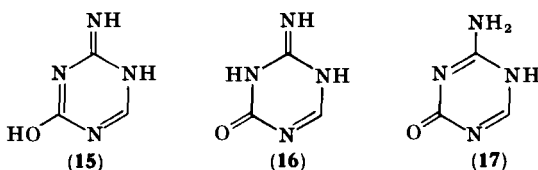
On the basis of the UV spectra of the neutral forms of cytosine and of the bathochromic and hypsochromic spectral shifts caused by protonation of cytosine and of its 1-methyl, 3-methyl, 5- and 6-halogeno derivatives, Wempen and Fox¹⁰⁵ have concluded that 6-chloro and 6-fluorocytosine were best represented by the form 3 in which the dissociable proton was affixed to N-3. 5-Halogenocytosines by contrast occur mainly as form 2.

2. Aza-Substitution: Tautomeric Shift 3 \rightarrow 6

The introduction of a nitrogen atom into cytosine (cytidine) yields 5-azacytosine (13) or 6-azacytosine (14). On the assumption that there



cannot be more than one labile hydrogen for an oxygen or nitrogen, the compounds are capable of existing in the forms similar to those of cytosine, namely 1–6. Additionally, 5-azacytosine can exist in the forms 15–17.



The physicochemical properties of azacytosines, and the corresponding azacytidines and their derivatives have been studied.¹¹⁶⁻¹²³ It was shown by IR, NMR, and UV spectroscopy^{116-118,123} that 6-azacytosine, *N,N*-dimethyl-6-azacytosine, and their 1-methyl derivatives as well as 6-azacytidine, possess the lactam-amine form **14**, like cytosine itself. Similar studies¹¹⁸ have shown that 3-methyl-6-azacytosine possesses the lactam-imine form **6**, in contrast to 3-methylcytosine, which has the lactam-amine form **3**.¹⁰²

Experimental evidence¹²² shows that 5-azacytosine and 5-azacytidine exist in the lactam-amine form, type **13**. Unfortunately, the tautomeric properties of 3-methyl-5-azacytosine have not been studied, so it is difficult to decide whether 5-aza-substitution in 3-methylcytosine causes a tautomeric shift toward the imine form.

The tautomeric studies of azacytosines are not so complete as those of cytosine itself. The contribution of other tautomeric forms of azacytosines to the tautomeric equilibrium has not been evaluated (because of lack of model tautomeric compounds). It appears that 6-aza-substitution causes a tautomeric shift from form **3** of cytosine toward its imine form, **6**. Thus, upon 6-aza-substitution the contribution of the imine tautomers to the tautomeric equilibrium of cytosine increases, while that of tautomers **3** decreases.

3. *Hydrogenation of Cytosine (5,6-Dihydrocytosine): Tautomeric Shift 2 → 6*

The tautomeric properties of 5,6-dihydrocytosine and its alkyl derivatives have been studied by means of several spectroscopic methods (UV, IR, NMR) as well as by the *pK* evaluation.^{124,125} IR evidence shows that the tautomeric forms with a lactim hydroxy group at C-2 position are unimportant. On the other hand, NMR spectra show that structures of the lactam-amine type with two hydrogens at the C-6 position and with a hydrogen at the N-3 atom were also unimportant.

¹¹⁶ J. Piřha and J. Beránek, *Collect. Czech. Chem. Commun.* **28**, 1507 (1963).

¹¹⁷ J. Piřha and J. Žemlička, *Collect. Czech. Chem. Commun.* **29**, 410 (1964).

¹¹⁸ J. Gut, J. Jonas, and J. Piřha, *Collect. Czech. Chem. Commun.* **29**, 1394 (1964).

¹¹⁹ A. Pískala and J. Gut, *Collect. Czech. Chem. Commun.* **28**, 1681 (1963).

¹²⁰ A. Pískala and J. Gut, *Collect. Czech. Chem. Commun.* **29**, 2794 (1964).

¹²¹ I. Flament, R. Promel, and R. H. Martin, *Bull. Soc. Chim. Belges* **73**, 585 (1964).

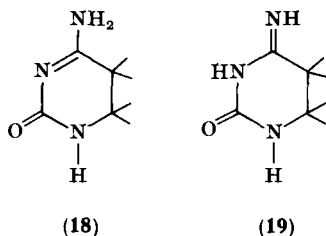
¹²² P. Piřhova, A. Pískala, J. Piřha, and F. Šorm, *Collect. Czech. Chem. Commun.* **30**, 1626 (1965).

¹²³ T. L. V. Ulbricht, *J. Chem. Soc.*, 6134 (1965).

¹²⁴ D. M. Brown and M. J. E. Hewlins, *J. Chem. Soc. C*, 2050 (1968).

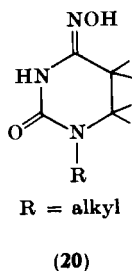
¹²⁵ D. M. Brown, *Pure Appl. Chem.* **18**, 187 (1969).

Brown and Hewlins¹²⁴ have concluded that only forms **18** and **19** are important for 1-alkyl-substituted 5,6-dihydrocytosine as for the parent molecule. Similar experimental evidence has shown that the dominant tautomer of 5,6-dihydrocytosine corresponds to a lactam-amine



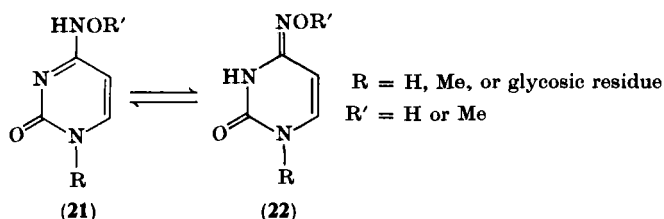
structure (**18**), but the tautomeric constant of forms **18** with respect to **19** was comparatively small ($K_{18,19} \approx 25$). The situation is different in chloroform: the IR spectra show that form **19** predominates in this solvent, although there is evidence of a small amount of form **18**. It is worth noting that, although the change from the amine to the imine form upon change of solvent polarity is unusual in N-heterocycles, the tautomeric shift observed by Brown and Hewlins is comprehensible because of the small value of the tautomeric constant in aqueous solution.

The tautomeric ratio of 25 in water for 5,6-dihydrocytosine should be compared with the value of $\sim 10^5$ for cytosine itself (see Table II). It thus appears that the hydrogenation of cytosine causes a substantial shift toward the imine form. A further shift toward the imine is observed when 5,6-dihydrocytosine is substituted at the amino group by a hydroxy group. It was shown¹²⁴ by UV spectra that 1-alkyl-substituted *N*⁴-hydroxy-5,6-dihydrocytosines exist in aqueous solution in the lactam(ox)imine form **20**.

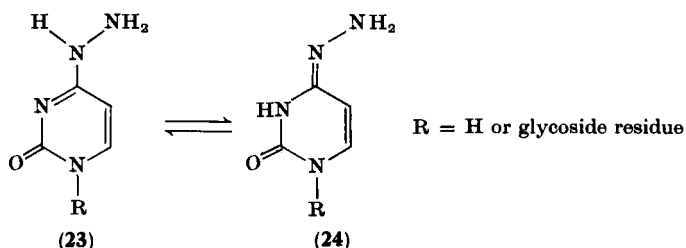


4. *Substitution of a Hydroxy, Methoxy, or Amino Radical at the Amino Group of Cytosine: Tautomeric Shift 2 \rightarrow 6*

One of the powerful chemical mutagens inducing point mutations is hydroxylamine, NH_2OH , and its N- and O-methyl derivatives.¹²⁵⁻¹³³ These react with the pyrimidine bases, and their reaction with cytosine (or cytidine) leads to the formation of several modified cytosines (or cytidines), among which are N^4 -hydroxycytosine (**21**, **22**, $\text{R} = \text{R}' = \text{H}$), and N^4 -methoxycytosine (**21**, **22**, $\text{R} = \text{H}$, $\text{R}' = \text{Me}$) and the



corresponding cytidines. A similar although weaker mutagenic agent is hydrazine. It too reacts only with the pyrimidine bases. The reaction of hydrazine, with cytosine (cytidine) yields among other things N^4 -aminocytosine (**23**, **24**).



Cytosines substituted at the amino group by hydroxy, methoxy, or amino groups are known to exist as mixtures of tautomers **21** or **23** and **22** or **24**, respectively. The tautomeric properties of these cytosines were

¹²⁶ J. Phillips and D. M. Brown, *Progr. Nucl. Acid. Res. Mol. Biol.* **7**, 349 (1968).

¹²⁷ E. Freese and E. B. Freese, *Radiat. Res. Suppl.* **6**, 97 (1966).

¹²⁸ N. K. Kochetkov and E. I. Budowsky, *Progr. Nucl. Acid. Res. Mol. Biol.* **9**, 403 (1969).

¹²⁹ C. Janion and D. Shugar, *Acta Biochim. Pol.* **12**, 337 (1965).

¹³⁰ C. Janion and D. Shugar, *Acta Biochim. Pol.* **15**, 107 (1968).

¹³¹ C. Janion and D. Shugar, *Acta Biochim. Pol.* **16**, 219 (1969).

¹³² C. Janion and D. Shugar, *Acta Biochim. Pol.* **18**, 403 (1971).

¹³³ C. Janion and D. Shugar, *Biochem. Biophys. Res. Commun.* **18**, 617 (1965).

studied by IR, NMR, and UV spectroscopy as well as by ionization constant measurements.^{134,135} From NMR spectra by Brown and Hewlins¹³⁴ the only possible forms for 1-substituted *N*⁴-hydroxy, *N*⁴-methoxy, or *N*⁴-aminocytosines are the 4-amine or 4-imine forms **21**–**24**. The IR and UV spectra indicate that *N*⁴-hydroxy and *N*⁴-methoxycytosines exist in solution predominantly in imine form **22** while *N*⁴-aminocytosine exists mainly in amine form **23**.

A comparison of the tautomeric constants in the series of *N*⁴-substituted cytosines indicates an interesting trend. As seen above, in the case of cytosine itself, the ratio of the tautomers of the amine type **2** to those of the imine type **6** is about 10⁵. In the case of *N*⁴-aminocytosine¹³⁴ the amine form **22** predominates by a factor of about 30, while *N*⁴-hydroxy compounds have mainly the imine form **21** with tautomeric constant ~ 10 [i.e., K_t (amine/imine) = $\sim 10^{-1}$]. Another study¹³⁶ of this constant gave the value of 25 [K_t (amine/imine) = $\sim 4 \times 10^{-2}$] in favor of the imine.

As we see, the contribution of the imine forms of *N*⁴-substituted cytosines to the tautomeric equilibrium becomes more important with respect to the amine forms with increase of the electronegativity of the *N*⁴-substituent in the series H, NH₂, OH(OMe).

In Table V are compiled the experimental data on the predominant tautomers of cytosine itself and some of its derivatives.

C. QUANTUM-MECHANICAL STUDIES

We now discuss the results of quantum-mechanical calculations which have been performed in order to predict the most stable tautomeric structures of cytosines.

This discussion requires the usual caution. Most important, the calculations refer in general to isolated molecules while the experimental data refer to the crystal or solution. A direct comparison between the two, although frequently made, must therefore be carried out with caution. This is particularly true when the different computed conformations differ little in energy, so that the effect of the environmental forces may be rather drastic. The same applies, *a fortiori*, to attempts at

¹³⁴ D. M. Brown and M. J. E. Hewlins, *J. Chem. Soc. C*, 1925 (1968).

¹³⁵ C. Janion, *Acta Biochim. Pol.* **19**, 261 (1972).

¹³⁶ E. D. Sverdlov, A. P. Krapivko, and E. I. Budowsky, *Khim. Geterosikl. Soedin.*, in press (quoted by Budowsky *et al.*¹³⁷).

¹³⁷ E. I. Budowsky, E. D. Sverdlov, and T. N. Spasokukotskaya, *FEBS Lett.*, **17**, 336 (1971).

TABLE V
PREDOMINANT TAUTOMERS OF CYTOSINES

Compound	Environment	Type of predominant tautomer	Experimental evidence	Remarks
Cytosine (cytidine)	Solid state	Lactam-amine (2)	X-Ray crystallography, IR, and Raman spectroscopy	—
	Aqueous solution	Lactam-amine (2)	IR, Raman, NMR, and UV spectroscopy, pK measurements	$K_{1.6}^2 \approx 10^4-10^5$, tautomer 3 more stable than tautomer 6 , alkylaminocytosines exist in form 2
	Nonaqueous solution	Lactam-amine (2)	IR, UV spectroscopy	Change of the proportions of tautomers on going from aqueous to nonaqueous solution
	Acetonitrile (nonaq. sol.)	Lactam-imine (6)	UV spectroscopy	Uncertain evidence (see text)
5-Fluorocytosine, 5-chlorocytosine	Aqueous solution	Lactam-amine (2)	UV spectroscopy	—
6-Fluorocytosine, 6-chlorocytosine	Aqueous solution	Lactam-amine (3)	UV spectroscopy	—
5-Azacytosine, 5-azacytidine	Aqueous solution	Lactam-amine (2)	IR, NMR, and UV spectroscopy	—
6-Azacytosine, 6-azacytidine	Aqueous solution	Lactam-amine (2)	IR, NMR, and UV spectroscopy	Tautomer 6 more stable than tautomer 3
5,6-Dihydrocytosine	Aqueous solution	Lactam-amine (2)	IR, NMR, and UV spectroscopy, pK measurements	$K^{2.6} = 25$
	Chloroform solution	Lactam-imine (6)	IR and UV spectroscopy	—
N^4 -Aminocytosine	Aqueous solution	Lactam-amine (2)	—	$K^{2.6} = 30$
N^4 -Hydroxycytosine, N^4 -methoxycytosine	Aqueous solution	Lactam-imine (6)	—	$K^{2.6} = 10^{-1}$ to 4.10^{-2}
N^4 -Hydroxy-5,6-dihydrocytosine	Aqueous solution	Lactam-imine (6)	—	—

correlation of the tautomeric ratios as measured, e.g., in solution, and the calculated energy differences between tautomeric forms.

Calculations on biological pyrimidines have been performed by practically all the available quantum-mechanical procedures including the nonempirical *ab initio* methods. But only in a few cases have attempts been made to interpret the stability of pyrimidine tautomers. We present here theoretical attempts by several investigators as well as some new results by us from the CNDO/2 method. The first application of the quantum-mechanical methods to the study of the stabilities of the cytosine tautomers was based on the π -Hückel molecular orbital (π -HMO) method. The method has been applied in particular to evaluate the *variation* of resonance energies upon tautomerization in the ground and excited state of cytosine,^{1,138,139} the π -energy difference between forms **2** and **6**¹⁴⁰ and to deduce the influence of aza-substitution on the tautomeric equilibrium^{141,122} (for related papers with an application of the π -HMO method see refs. 5, 140, 142, 143; and for π -SCF MO approach, see ref. 144). It must be emphasized that computations limited to the π -electron systems (π -HMO, π -SCF MO) are only significant to the problem of tautomerism if the energies of the σ -bonds in tautomers are invariant. They may only be used, following a well documented procedure,¹ to give information on the *relative tendencies* of a series of related molecules, such as the nucleic acid bases, to undergo amine-imine (or lactam-lactim) tautomerism.

Table VI collects the theoretical quantities appropriate to the description of the tautomeric stability of cytosine, computed by methods including both π - and σ -electrons. We have added to it the results of a π -SCF MO approach (including σ -polarization effects) on heats of atomization of different tautomeric forms of cytosine. Bodor *et al.*¹⁴⁹ have related the heat of atomization to the stability of the tautomers, and found that the most stable structure of the molecule is the amine-lactam **2** having the greatest heat of atomization (59.707 eV). They predict on this basis the following order of stability: **2** > **3** > **6** > **1**.

¹³⁸ B. Pullman and A. Pullman, *Biochim. Biophys. Acta* **64**, 403 (1962).

¹³⁹ A. Pullman and B. Pullman, *Biochim. Biophys. Acta* **74**, 269 (1963).

¹⁴⁰ T. A. Hoffman and J. Ladik, *Advan. Chem. Phys.* **7**, 84 (1964).

¹⁴¹ A. Pullman, *Biochim. Biophys. Acta* **87**, 365 (1964).

¹⁴² V. I. Poltev and B. I. Sukhorukov, *Biofizika* **16**, 5 (1971).

¹⁴³ B. I. Sukhorukov and V. I. Poltev, *Biofizika* **9**, 148 (1964).

¹⁴⁴ N. Dupuy-Mamelle and B. Pullman, *J. Chim. Phys.* **64**, 708 (1967).

¹⁴⁵ H. Berthod and A. Pullman, *Biopolymers* **2**, 483 (1964).

¹⁴⁶ H. Berthod and A. Pullman, *J. Chim. Phys.* **62**, 942 (1965).

¹⁴⁷ B. Pullman, *J. Chem. Phys.* **43**, S233 (1965).

¹⁴⁸ V. I. Danilov, *Biofizika* **12**, 540 (1967).

¹⁴⁹ N. Bodor, M. J. S. Dewar, and A. J. Hart, *J. Amer. Chem. Soc.* **92**, 2929 (1970).

TABLE VI
THEORETICAL QUANTITIES^a CHARACTERIZING TAUTOMERIC STABILITY
OF CYTOSINE

Method	References	Quantity ^b (kcal/mole)
π -HMO + σ -Del Re	Berthod and Pullman ¹⁴⁵⁻¹⁴⁷	$\Delta E^{2,6} = -8.0$
π -SCF MO + σ -Del Re	Danilov ^{148,6}	$\Delta H_{S_0}^{2,6} = 12.7$, $\Delta H_{S_1}^{2,6} = 30.5$ $\Delta H_{(+)}^{2,6} = 25.3$, $\Delta H_{(-)}^{2,6} = 20.4$
π -SCF MO ^c	Bodor <i>et al.</i> ¹⁴⁹	$\Delta H_{\alpha}^{2,3} = -0.7$ $\Delta H_{\alpha}^{2,6} = -2.2$ $\Delta H_{\alpha}^{2,1} = -4.7$
CNDO/2 ^d	Present work	$\Delta E^{2,1} = -2.01$ $\Delta E^{2,3} = -10.65$ $\Delta E^{2,6} = -13.90$
CNDO/2 CI	Bertrán <i>et al.</i> ¹⁵⁰	$\Delta E_{S_1}^{2,6} - \Delta E_{S_0}^{2,6} = -1.04$ $\Delta E_{T_1}^{2,6} - \Delta E_{S_0}^{2,6} = 0.93$

^a For the theoretical interpretation (π -HMO, π -SCF MO) of the *relative tendency* of cytosines to undergo tautomerization see text.

^b Abbreviations: $\Delta H_{\alpha}^{i,j}$, difference between heats of atomization of tautomers (i) and (j); $\Delta H^{2,6}$, changes of enthalpy upon tautomeric conversion $2 \rightarrow 6$; $\Delta H^{i,j}$, difference between the total ($\pi + \sigma$)-electron energies (π -HMO + σ -Del Re) or total energies (CNDO/2) of tautomers (i) and (j). All values refer to the ground state of cytosine (S_0) unless otherwise indicated.

^c The method includes σ -polarization.¹⁵¹

^d For other CNDO/2 calculations on tautomeric stability of cytosine, see refs. 14, 152, 153. In all these calculations the same geometry of the ring has been used for different tautomers.

It is interesting that the calculated energy of the σ bonds (including the lone-pair electrons) by means of the σ -Del Re method^{146,154,155} favors slightly the imine form **6** of cytosine, but the summation of ΔE_{π} and ΔE_{σ} leads to the conclusion that the form **2** should be the most stable one.¹⁴⁵⁻¹⁴⁷

The π -SCF MO method and the Del Re procedure for σ -electrons have been applied by Danilov¹⁴⁸ to evaluate the enthalpy changes on tautomeric conversion $2 \rightarrow 6$ in the ground state and the first excited singlet state for cytosine and its anionic and cationic forms. The results show that although in the ground state of cytosine the tautomeric

¹⁵⁰ J. Bertrán, O. Chalvet, and R. Daudel, *An. Fis.* **66**, 247 (1970).

¹⁵¹ M. J. S. Dewar and T. Morita, *J. Amer. Chem. Soc.* **91**, 796 (1969).

¹⁵² H. Fujita, A. Imamura, and C. Nagata, *Bull. Chem. Soc. Jap.* **42**, 1467 (1969).

¹⁵³ O. M. Sorarrain and E. A. Castro, *Chem. Phys. Lett.* **19**, 422 (1973).

¹⁵⁴ G. Del Re, *J. Chem. Soc.*, 4031 (1958).

¹⁵⁵ G. Del Re, in "Electronic Aspects of Biochemistry" (B. Pullman, ed.), p. 221. Academic Press, New York, 1964.

equilibrium already greatly favors the amine form, upon excitation or on going to ionic forms the equilibrium is shifted still more toward forms **2**. This last result is in general agreement with the recent experimental evidence⁹⁹ indicating no considerable displacement in tautomeric equilibrium (strictly speaking experimental evidence⁹⁹ shows a slight shift toward forms **6**, while the calculations¹⁴⁸ indicate a slight shift toward forms **2**).

CNDO/2 CI calculations performed by Bertrán *et al.*¹⁵⁰ to evaluate the variation of the tautomeric constant $K_t^{2,6}$ upon excitation do predict a shift toward the rare imine forms **6** in the first excited singlet state, and a shift toward the normal form **2** in the first triplet state.

The CNDO/2 method has also been applied by several investigators to the study of the stability of cytosine tautomers in their ground states.^{14,150,152,153} At this point it is worth recalling the difficulty (see ref. 3) connected in such studies with the uncertainty as to the geometry of the rare tautomeric forms (because of lack of experimental data). The quantitative results of the CNDO/2 calculations depend appreciably on the assumed geometrical structures of these rare forms. Nevertheless, all CNDO/2 calculations (Table VI and refs. 14, 152, 153) predict lactam-amine tautomer **2** to be more stable than lactam-imine **6**. The energy difference between these tautomers has been evaluated to be of the order of 13.9–26.6 kcal/mole, depending on the geometry of the structures.

Breen and Flurry¹⁴ have investigated the stability of cytosine tautomers **1**, **2**, **3**, and **6** by means of the CNDO/2 method using different geometrical assumptions. Maintaining the same geometry (from Barker and Marsh¹¹) for the heavy atoms for all tautomers, they find the lactim-amine tautomer **1** to be the most stable, tautomer **2** to be 0.024 eV less stable than **1** and lactam-imine tautomer **6** to be the least stable. Calculations performed on nonplanar tautomers having out-of-plane hydrogens of the amino group show the same order of stability. Calculations in which the exocyclic bonds C–O and C–N were scaled, but the angular geometries of the tautomers retained, gave again the same order of stability. Calculations performed with all the coordinates for each tautomer scaled gave, however, the tautomer **2** as the most stable. Lactim-amine tautomer **1** was the next, but higher in energy by 1.5 kcal/mole. The relative energetic positions of the other two tautomers were the same as in the unscaled tautomers.

It is interesting that lactim-imine tautomers **5** and **4** appear to have considerably higher energies than tautomers **2** or even tautomer **6**.¹⁵⁶

¹⁵⁶ B. L. Lesyng, M. Sci. Thesis, Univ. of Warsaw (1972), and unpublished results.

On the other hand, all CNDO/2 calculations predict that the tautomer **2** should be more stable than tautomer **3**, and this last form more stable than the form **6**. This prediction is in good agreement with the experimental evidence (Table II).

One point connected with these calculations deserves additional comment. As stated above, the results of the CNDO/2 energy calculations depend appreciably on the geometry assumed for the tautomeric forms. In a few cases^{14,152,156,157} unsatisfactory results were obtained in predicting the position of the lactam-lactim equilibrium in N-heterocyclic molecules, owing to uncertainty in the geometry of the hydroxy group,^{3,157} i.e., the C–O and O–H bond lengths. Usually, the calculations are performed with 1.4–1.46 Å and 0.9–1.0 Å, respectively. Pullman and Pullman³ have made a study of the relative stability of the lactim form of guanine with respect to its lactam form as a function of the lengths of the C–O and O–H bonds. They showed that in order to interpret correctly the relative stabilities of guanine tautomers one has to use bond lengths 1.36 and 0.85 Å, respectively (compare also the study of the lactam-lactim tautomerism in pyridones and pyrimidones¹⁵⁷). More recently detailed crystallographic information became available about the geometry of the O–H substituent in the lactim form of pyridinols.^{8,9} This geometry ($r_{\text{C-O}} \approx 1.33$ and $r_{\text{O-H}} = 0.86$ Å) is close to that used in the Pullmans' studies on the lactim-lactam tautomerism of guanine.³ The same values of the C–O and O–H bond lengths have also been used in our calculation on the lactim form of cytosine.

Table VII contains the results of the CNDO/2 calculation¹⁵⁸ on the energy of cytosine tautomers **2**, **3** or **6** and of some derivatives. It can be seen that the calculated energy shifts are in agreement with the effect of substitution on the tautomeric equilibrium of cytosine discussed in Section II, B. Thus, a 5-fluoro substituent causes a small tautomeric shift toward forms **3** ($\Delta E_{5-\text{F}-\text{Cyt}}^{2,3} - \Delta E_{\text{Cyt}}^{2,3} = 2.98$ kcal/mole) or **6** ($\Delta E_{5-\text{F}-\text{Cyt}}^{2,6} - \Delta E_{\text{Cyt}}^{2,6} = 4.87$ kcal/mole), while a 6-fluoro substituent causes a large shift toward form **3** ($\Delta E_{6-\text{F}-\text{Cyt}}^{2,3} - \Delta E_{\text{Cyt}}^{2,3} = 10.33$ kcal/mole) and a negligible shift toward form **6**, ($\Delta E_{6-\text{F}-\text{Cyt}}^{2,6} - \Delta E_{\text{Cyt}}^{2,6} = 1.63$ kcal/mole). These conclusions have been confirmed by a very recent evaluation of the singlet-singlet transition energies¹⁵⁹ by means of the π -SCF MO CI method. These calculations predict that a 5-fluoro substituent in the cytosine tautomers **2**, **3** and **6** should shift the first

¹⁵⁷ M. Berndt, J. S. Kwiatkowski, J. Budziński, and B. Szczodrowska, *Chem. Phys. Lett.* **19**, 246 (1973).

¹⁵⁸ J. S. Kwiatkowski and B. Pullman, *Acta. Phys. Pol.* **A45**, 693 (1974).

¹⁵⁹ B. L. Lesyng, *Studia Biophys.*, in press.

TABLE VII
EFFECT OF SUBSTITUENT ON THE STABILITY OF TAUTOMERIC FORMS OF CYTOSINE

Substituent	Theoretical data ^a		Experimental data ^b	
	$\Delta E^{2,3}$	$\Delta E^{2,6}$	$K_t^{2,3}$	$K_t^{2,6}$
None (cytosine itself)	-10.65	-13.90	$\sim 10^3$	$\sim 10^{4,7}$
5-Fluoro	-7.87	-9.03	$> 1^c$	—
6-Fluoro	-0.32	-12.27	$< 1^c$	—
<i>N</i> ⁴ -Amino	—	-1.62	—	30
<i>N</i> ⁴ -Hydroxy	—	-0.07	—	$\sim 10^{-1}$ — 4×10^{-2}
5,6-Dihydro	—	-1.0 ^d	—	~ 25 (in water) 10^{-1} (in chloroform)

^a Differences between CNDO/2 energies of tautomers 2, 3 and 2, 6, respectively. All values in kilocalories per mole.

^b Compare Table II. $K_t^{i,j}$ stands for tautomeric ratio of forms (i) to (j).

^c Dominating tautomers 2 and 3 for 5-fluoro and 6-fluorocytosine, respectively.

^d From ref. 3. For cytosine itself the $\Delta E^{2,6}$ value was calculated³ to be equal to -15 kcal/mole.

absorption band of cytosine toward longer wavelengths (bathochromic effect), while a 6-fluoro substituent should cause a shift toward shorter wavelengths (hypsochromic effect). The magnitude of the bond shift is smaller in the latter case than in the former. Experimentally, Wempen and Fox¹⁰⁵ have measured the shifts upon both 5- and 6-fluoro substitution. The observed spectral shifts agree with the theoretical data only when the observed bands are attributed to the absorption of tautomers 2 in cytosine and 5-fluorocytosine, and to that of tautomer 3 in 6-fluorocytosine.

Predicted tautomeric shifts also correlate satisfactorily with the experimental shifts observed in the cytosine, *N*⁴-amino- and *N*⁴-hydroxycytosine series. In accordance with the experimental evidence, the calculations predict a significant tautomeric shift toward imine form 6 upon amino or hydroxy substitution at the amino group of cytosine. Previously reported calculations³ also gave a satisfactory interpretation of the tautomeric shift caused by hydration of cytosine.

III. Electronic Structure of the Ground State of Cytosines

This section is devoted to the presentation of the essential physico-chemical properties of cytosine and some of its derivatives and to the theoretical interpretation of these properties. Since the tautomeric

equilibrium of cytosine is displaced very strongly toward the lactam-amine form **2** and there is relatively very little experimental information available about the other tautomers, our discussion is in general restricted to this essential form. Some properties of the rare forms, however, are also presented.

A. THE GEOMETRY OF CYTOSINE

Abundant information on the geometrical structure of cytosine, i.e., on the bond angles and lengths, is available from X-ray crystallographic investigations (for reviews, see refs. 7, 27, 160–168). Comparison of the crystal data from different publications shows that the different distances and angles differ significantly among themselves in the different studies compared with the evaluated standard deviations of these quantities.⁷ The criterion of reliability chosen by Voet and Rich⁷ in the latest review was that the estimated standard deviations of the bond lengths and the bond angles of the reference molecules should be less than 0.05 Å and 3°, respectively.

We have performed a similar averaging of the crystal data, in which, in addition to the crystallographic structures chosen by Voet and Rich, some more recent crystal structures were taken into consideration.^{20,22} These new calculated average values of the bond lengths and angles compare quite well with the averages determined by Voet and Rich.⁷

The MO methods have been used to calculate the π -electronic bond orders in unprotonated cytosine, and the bond lengths have been calculated on the basis of these quantities in the customary way.^{168a} The qualitative agreement (Fig. 2) between the theoretical and experimental values is, in general, good, the best being obtained by means of the simple π -HMO method. The π -bond orders or total bond overlap populations calculated by different methods can be found in several papers: π -HMO calculations on cytosines, see reviews^{1,140,170–172}; π -SC

¹⁶⁰ M. Spencer, *Acta Crystallogr.* **12**, 50 (1959).

¹⁶¹ M. Spencer, *Acta Crystallogr.* **12**, 66 (1959).

¹⁶² L. Pauling and R. B. Corey, *Arch. Biochem. Biophys.* **65**, 164 (1956).

¹⁶³ J. Kendrew and M. Perutz, *Annu. Rev. Biochem.* **26**, 327 (1957).

¹⁶⁴ A. Rich and D. W. Green, *Annu. Rev. Biochem.* **30**, 93 (1961).

¹⁶⁵ J. Kraut, *Annu. Rev. Biochem.* **34**, 247 (1965).

¹⁶⁶ M. Sundaralingam, *J. Amer. Chem. Soc.*, **87**, 599 (1965).

¹⁶⁷ D. R. Davies, *Annu. Rev. Biochem.* **36**, 321 (1967).

¹⁶⁸ J. Donohue, *Arch. Biochem. Biophys.* **128**, 591 (1968).

^{168a} Recent π -SC HMO (improved ω -technique) calculations¹⁶⁹ did not change the correlation between the calculated and experimental bond distances in cytosine.

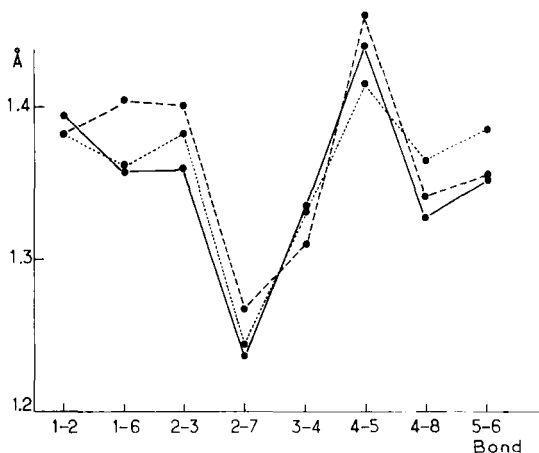


FIG. 2. Comparison between experimental⁷ (—) bond distances of cytosine and those calculated by means of the π -Hückel molecular orbital method¹ (····) and the π -self-consistent field MO method¹⁴⁹ (---).

HMO (ω -technique) calculations¹⁶⁹ on cytosine, forms **1** and **2**, 1-methylcytosine; π -SCF MO calculations on cytosine, forms **2**,^{104,144,156,171,173-180} **6**,^{104,144,156,177,178} **3**,^{104,156,178} **1**, **4** and **5**,^{156,178} 5,6-dihydro-cytosine, forms **2** and **6**,^{144,181} guanine-cytosine base pair^{171,175,182-186}

¹⁶⁹ Y. G. Smeyers and G. Delgado-Barrio, *An. Real Soc. Espan. Fis. Quim. Ser. B* **68**, 25 (1972).

¹⁷⁰ J. I. Fernández-Alonso, *Advan. Chem. Phys.* **7**, 3 (1964).

¹⁷¹ S. Fraga and C. Valdemoro, *Struct. Bonding (Berlin)* **4**, 1 (1968).

¹⁷² N. K. Kochetkov and E. I. Budovskii (eds.), "Organic Chemistry of Nucleic Acids," Chapter 3. Plenum Press, London, 1971.

¹⁷³ V. A. Kuprievich, V. I. Danilov, and O. V. Shramko, *Teor. Eksp. Khim.* **2**, 734 (1966).

¹⁷⁴ A. Imamura, H. Fujita, and C. Nagata, *Bull. Chem. Soc. Jap.* **40**, 21 (1967).

¹⁷⁵ A. Imamura, H. Fujita, and C. Nagata, *Bull. Chem. Soc. Jap.* **40**, 522 (1967).

¹⁷⁶ A. Pullman, in "The Triplet State" (A. B. Zahlan, ed.), p. 515. Cambridge Univ. Press, London and New York, 1967.

¹⁷⁷ T. Miyata, H. Suzuki, and S. Yomosa, *J. Phys. Soc. Jap.* **25**, 1428 (1968).

¹⁷⁸ T. L. Kunii and H. Kuroda, *Rep. Computer Center, Univ. Tokyo* **1**, 227 (1968).

¹⁷⁹ V. I. Danilov, O. V. Shramko, and G. G. Dyadyusha, *Biofizika* **12**, 544 (1967).

¹⁸⁰ C. Valdemoro and S. Fraga, Technical Report TC-6701, Dep. Chem. Univ. of Alberta (1967).

¹⁸¹ B. Pullman and B. Dupuy, *C.R. Acad. Sci.* **262**, 2773 (1966).

¹⁸² R. Rein and J. Ladik, *J. Chem. Phys.* **40**, 2466 (1964).

¹⁸³ R. Rein and F. E. Harris, *J. Chem. Phys.* **41**, 3393 (1964).

¹⁸⁴ V. I. Danilov, V. A. Kuprievich, and O. V. Shramko, *Biofizika* **12**, 186 (1967).

¹⁸⁵ C. Valdemoro and S. Fraga, Technical Report TC-6702, Dep. Chem., Univ. of Alberta (1967).

¹⁸⁶ V. I. Danilov, N. V. Zheltovsky, V. V. Oglobin, and V. I. Pechenaya, *J. Theor. Biol.* **30**, 559 (1971).

(for the π -bond orders of the C(5)–C(6) bond in cytosine and 5-methylcytosine, see refs. 187–189); π -SCF MO + σ -Del Re calculations¹⁹⁰ on cytosine, form 6, and on four pairs of 2-aminopurine (amine and imine forms) with cytosine (forms 2 and 6); EHT calculations¹⁹¹ on cytosine and cytidine.

Cytosine as well as the other heterocyclic nucleic acid bases are quasiaromatic compounds, expected to be planar. The experimental evidence shows that this is not strictly so, but the deviations of the ring atoms of cytosine from planarity are, in general, small, and in most cases within the limits of the experimental accuracy. Oxygen and amino groups, and the atoms of substituents, when present, appear to deviate more from planarity. In all the quantum-mechanical studies the cytosine ring has been assumed to be planar.

B. VIBRATIONAL SPECTRA OF CYTOSINE

As mentioned in Section II the IR and Raman spectra of cytosine and of some of its derivatives have been reported in detail. These spectra have been particularly useful for the elucidation of the structure of the predominant tautomer.

More recently, IR and Raman spectroscopy have been used by Susi *et al.*¹⁹² (cf. also ref. 193) to investigate the vibrations of cytosine and cytosine- d_3 , and assignments have been given for the in-plane fundamental modes. A valence force field for cytosine has also been proposed and employed to reproduce the observed frequencies with an average error of ca. 10 cm^{-1} ($\sim 1.0\%$).

Up to now, quantum-mechanical methods have not been applied to the study of the vibrational spectra of cytosine (see Section V, however, for an interpretation of the hydrogen bond vibrational spectra of the guanine-cytosine base pair).

¹⁸⁷ G. G. Dyadyusha, V. I. Danilov, and O. V. Shramko, *Mol. Biol.* **1**, 539 (1967).

¹⁸⁸ V. I. Danilov, Yu. A. Kruglyak, V. A. Kuprievich, and V. V. Oglogin, *Theor. Chim. Acta* **14**, 242 (1969).

¹⁸⁹ Yu. A. Kruglyak, V. I. Danilov, V. A. Kuprievich, and V. V. Oglobin, *Theor. Eksp. Khim.* **6**, 33 (1970).

¹⁹⁰ V. I. Danilov, Yu. A. Kruglyak, V. A. Kuprievich, and O. V. Shramko, *Biofizika* **12**, 726 (1967).

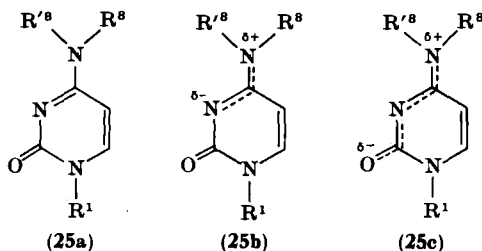
¹⁹¹ F. Jordan and B. Pullman, *Theor. Chim. Acta* **9**, 242 (1968).

¹⁹² H. Susi, J. S. Ard, and J. M. Purcell, *Spectrochim. Acta, Part A* **29**, 725 (1973).

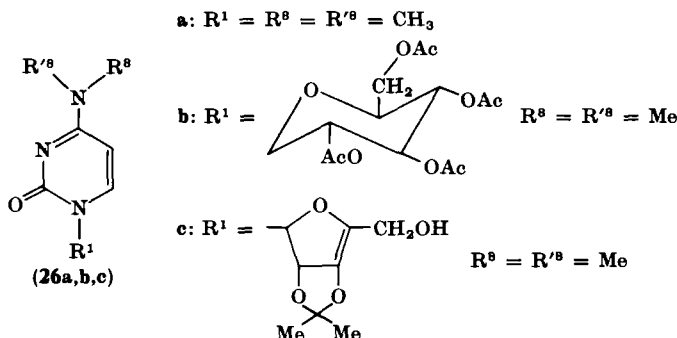
¹⁹³ V. Ya. Maleev and A. E. Stanevich, in "Spektroskopiya Tverdogo Tela" (S. E. Frish, ed.), p. 95, Izd. "Nauka," 1969.

C. RESTRICTED ROTATION ABOUT THE EXOCYCLIC C-N BOND

The amino groups of the nucleic acid bases may, in principle, undergo relatively free rotation. In fact, however, they must be considered as having a significant amide character as a result of a partial double-bond character of the C-N bond due to resonance structures of types **25b** and **25c**.



Rotational restriction of the amino group has been observed by the NMR spectroscopy technique in a number of cytosines in solution as well as in the crystalline state.^{64,86,88,89,194} Shoup *et al.*^{89,90} measured the activation parameters for the rotation of the dimethylamino group in N⁸-dimethylcytosine derivatives. With one exception, the range of activation energies is 15–18 kcal/mole. The activation energies found for **26a** and **26b** are about twice those reported by Martin and Reese¹⁹⁵ for **26c**. In this last case, however, the method by which the activation energy was obtained has not been described (usually approximate



methods for obtaining rate constants from NMR spectra give too low activation energies), so probably the values obtained by Shoup *et al.* are more reliable. Table VIII collects several activation parameters for the

¹⁹⁴ R. R. Shoup, H. T. Miles, and E. D. Becker, *Biochem. Biophys. Res. Commun.* **23**, 194 (1966).

¹⁹⁵ D. M. G. Martin and C. B. Reese, *Chem. Commun.*, 1275 (1967).

TABLE VIII
ACTIVATION PARAMETERS^a FOR THE ROTATION ABOUT THE EXOCYCLIC C-N BOND OF CYTOSINES

Compound	State	E_a (kcal/mole)	k_{298} (sec ⁻¹)	ΔS^\ddagger (e.u.)	ΔF_{298}^\ddagger (kcal/mole)	ΔF_c^\ddagger (kcal/mole)	References
1-Methylcytosine	Dimethyl- formamide-d ₇	—	138	—	—	—	88
1- <i>N</i> ⁸ , <i>N</i> ⁸ -Trimethylcytosine (26a)	CDCl ₃	17.6	90	7.5	14.8	14.9	89
	CD ₃ CN	15.1	123	-0.5	14.6	14.6	—
	CD ₃ OD	15.7	48	0.2	15.2	15.1	—
	SO ₂	11.5	1050	-8.1	13.3	12.7	—
<i>N</i> ⁸ , <i>N</i> ⁸ -Dimethyl-1-(2',3',4',6'- tetraacetyl-D-glucopyranosyl)cytosine (26b)	CDCl ₃	17.3	4.5	0.5	16.6	16.5	89
	CD ₃ CN	18.1	8.8	4.4	16.2	16.2	—
2',3'- <i>O</i> -Isopropylidene- <i>N</i> ⁸ , <i>N</i> ⁸ -dimethylcytidine (26c)		8.6	—	—	—	—	195

^a Notation: E_a , activation energy; k_{298} , rate constant at 298°K; ΔS^\ddagger , entropy of activation; ΔF_{298}^\ddagger and ΔF^\ddagger , free energies of activation at 298°K and at coalescence, respectively.

rotation of the $\text{NR}_8\text{R}'_8$ group in cytosine derivatives. Among these activation parameters, the activation energy E_a was the subject of a theoretical treatment by means of the all valence-electrons methods. We have carried out¹⁵⁸ PCILO calculations for the barrier of rotation about the exocyclic C(4)–N(8) bond in several cytosines (Table IX). It can clearly be seen that the computations predict restricted rotation of the amino group in cytosine itself as well as in several methyl derivatives. It can also be seen that the barrier height to rotation is sensitive to methyl substitution at positions C-5 or N-8, but not to substitution at position N-1 or C-6. The CNDO/2 calculations predict the same dependence of the barrier heights on the position of substituent. The order of decreasing barrier heights in rotation in cytosine derivatives shown by both methods is cytosine > N^8 -methylcytosine > N^8, N^8 -dimethylcytosine.

We can also see that the theoretical values of the barrier heights to rotation of the NMe_2 group in N^8, N^8 -dimethylcytosine are 15–16 kcal/mole, in very good agreement with the experimental data (15–18 kcal/mole).

An analysis of the NMR spectra of monomethylamino derivatives of cytosines shows that the rotation of the NHMe group is also restricted. From the corresponding peak heights of the NMR spectra, Shoup *et al.*⁸⁹ have evaluated the relative concentrations of 96/4 and 94.7/5.3 for the conformers of 1-methyl-4-methylaminopyrimid-2-one and 2-methoxy-1,5-dimethyl-4-methylaminopyrimidine having the NHMe group *syn* and *anti* to N-3. The corresponding associated free energy differences are 1.6 and 1.5 kcal/mole, respectively. Our calculations predict correctly that the *syn* conformers are more stable than the *anti* ones in the methylaminocytosines, and the calculated energy difference ΔE between these two conformers of 1.0 and 0.9 kcal/mole for N^8 -methyl and 6, N^8 -dimethylcytosine, respectively, can be compared with the corresponding values⁸⁹ of the free energy differences of 1.6 and 1.5 kcal/mole. The NMR evidence⁸⁹ shows that 5, N^8 -dimethylcytosine exists almost exclusively in one conformation, almost certainly with the N^8 -methyl *syn* to N-3. The energies of the conformers of the molecule calculated by the PCILO method predict correctly this experimental fact (see Table VIII). A conformational study¹⁹⁸ of N-6-substituted

¹⁹⁶ C. N. R. Rao, in "Conformation of Biological Molecules and Polymers" (E. D. Bergmann and B. Pullman, eds.), p. 107, Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1973.

¹⁹⁷ K. G. Rao and C. N. R. Rao, *J. Chem. Soc. Perkin Trans. 2*, 889 (1973).

¹⁹⁸ H. Berthod and B. Pullman, *C.R. Acad. Sci. Ser. D* **276**, 1767 (1973).

TABLE IX
CALCULATED VALUES FOR BARRIER OF ROTATION AND BARRIER HEIGHTS

Compound	Energy ^a (kcal/mole), with respect to the individual global minimum, from PCILO calculation. ^c Angle of rotation, Φ (C4-N8), in degrees							Barrier heights ^b to rotation (kcal/mole) from CNDO/2 calcu- lation (Rao ^{196,197})
	0	30°	60°	90°	120°	150°	180°	
Cytosine	0	4.64	13.66	<i>18.04</i>	13.66	4.64	0	25
1-Methylcytosine	0	4.66	13.70	<i>18.10</i>	13.70	4.66	0	20
5-Methylcytosine	0	4.52	13.41	<i>17.73</i>	13.41	4.52	0	16
6-Methylcytosine	0	4.66	13.73	<i>18.13</i>	13.73	4.66	0	20
<i>N</i> ⁸ -Methylcytosine	1.02	5.25	13.25	<i>17.38</i>	13.51	4.83	0	17
5, <i>N</i> ⁸ -Dimethylcytosine	<i>23.22</i>	18.73	13.98	<i>17.01</i>	13.19	4.74	0	—
6, <i>N</i> ⁸ -Dimethylcytosine	0.89	5.18	13.34	<i>17.50</i>	13.59	4.85	0	17
<i>N</i> ⁸ , <i>N</i> ⁸ -Dimethylcytosine	0	4.20	12.01	<i>15.83</i>	12.01	4.20	0	15

^a Italicized figures are the barrier heights to rotation.

^b Barrier heights to rotation in 1-*N*⁸-dimethylcytosine was calculated^{196,197} as 17 kcal/mole.

^c Calculations were obtained in collaboration with Dr. B. Mély.

adenines by the PCILO method shows also that the conformers with the N^6 -methyl or N^6 -(Δ^2 -isopentenyl) *syn* to N-1 are the more stable ones.

D. DISTRIBUTION OF ELECTRON DENSITY IN CYTOSINES

The ground-state wave function of cytosine has been calculated by practically all the semiempirical as well as nonempirical methods. Here, we shall discuss the application of these methods to interpret the experimental quantities that can be calculated from the molecular orbitals of cytosines and are related to the distribution of electron densities in the molecules. The simplest π -HMO method yielded a great mass of useful information concerning the structure and the properties of biological molecules including cytosines. The reader is referred to the book¹ "Quantum Biochemistry" for the application of this method to interpret the physicochemical properties of biomolecules. Here we will restrict our attention to the results of the π -SCF MO and the all-valence or all-electron treatments of cytosines.

1. Distribution of π -Electrons, σ -Electrons, and the Total Electron Density

Several methods of quantum chemistry have been applied to calculate the charge distributions in cytosine and some of its derivatives.

The results can be found as follows: for π -HMO calculations see reviews^{1,140,170-172}; π -SC HMO (improved ω -technique) calculations¹⁶⁹ on forms 1 and 2 of cytosine, 1-methylcytosine; π -SCF MO calculations on cytosine, forms 2,^{104,144,149,156,171,173-178,180,198-206} 6,^{104,140,144,149,156,177,178} 3,^{104,156,178} 1, 4, and 5,^{104,156} cationic and anionic forms of cytosine,^{156,177,203,207} amine and imine forms of 5,6-dihydrocytosine,^{144,181} 1-, 3-, 5-methyl and N^8 -methylcytosine,²⁰⁸ 5- and 6-substituted cytosine²⁰⁵ by F, Cl, Br, I, OH, OCH₃, SH, NH₂, CH₃, and COOH,

¹⁹⁹ A. Veillard and B. Pullman, *C.R. Acad. Sci.* **253**, 2277 (1961).

²⁰⁰ A. Veillard and B. Pullman, *J. Theor. Biol.* **4**, 37 (1963).

²⁰¹ C. Nagata, A. Imamura, Y. Tagashira, and M. Kodama, *Bull. Chem. Soc. Jap.* **38**, 1638 (1965).

²⁰² J. Ladik and K. Appel, *Theor. Chim. Acta* **4**, 132 (1966).

²⁰³ V. A. Kuprievich, *Int. J. Quant. Chem.* **1**, 561 (1967).

²⁰⁴ C. Nagata and O. Mårtensson, *J. Theor. Biol.* **19**, 133 (1968).

²⁰⁵ J. Ladik and G. Biczó, *Acta Chim. Acad. Sci. Hung.* **62**, 401 (1969).

²⁰⁶ J. C. Parker, J. S. Avery, J. Ladik, and G. Biczó, *Int. J. Quant. Chem.* **3**, 79 (1969).

²⁰⁷ V. A. Kuprievich, *Theor. Eksp. Khim.* **3**, 66 (1967).

²⁰⁸ A. Denis and H. Berthod, *J. Chim. Phys.* **65**, 1815 (1968).

reaction products of cytosine with hydroxylamine,²⁰⁴ 5-methyl and 5-hydroxymethyl substituted cytosines and their 4-hydroxylaminoderivatives,²⁰⁴ guanine-cytosine base pair^{175,182-186} and its cation and anion²⁰⁹ (for the charge densities at C-5 and C-6 positions in cytosine and 5-methylcytosine see^{6,187,189}); π SCF MO + σ -Del Re calculations on cytosine, form 6,¹⁹⁰ 1-methylcytosine, forms 2 and 6,²¹⁰ four pairs of 2-aminopurine (amine and imine forms) with cytosine (forms 2 and 6)¹⁹⁰; EHT calculations on cytosine and cytidine¹⁹¹; IEHT calculations on cytosine²¹¹⁻²¹³ and its protonated form²¹³; CNDO/2 calculations on cytosine form 2,^{156,197,214,215} 1-, 5-, 6-, N⁸-methyl and N⁸-dimethylcytosine¹⁹⁷ (cf. also Labhart and Herrmann²¹⁶ on SCF MO calculations, including π and σ electrons within electrostatic approximation, on cytosine), and see Figs. 5 and 6 for CNDO/2 calculations on different tautomers of cytosine and its derivatives, charges on atoms involved in hydrogen bonds of guanine-cytosine base pair²¹⁷; *nonempirical* calculations on cytosine.²¹⁸⁻²²⁰

The charge distributions in cytosine have been previously reviewed in several articles and books.^{1,6,140,170-172,221-227} These include the

²⁰⁹ V. I. Danilov, V. A. Kuprievich, and O. V. Shramko, *Biofizika* **12**, 606 (1967).

²¹⁰ G. E. Bass and L. J. Schaad, *J. Amer. Chem. Soc.* **93**, 4585 (1971).

²¹¹ A. Pullman, E. Kochanski, M. Gilbert, and A. Denis, *Theor. Chim. Acta* **10**, 231 (1968).

²¹² R. Rein, N. Fukuda, G. A. Clarke, and F. E. Harris, *J. Theor. Biol.* **21**, 88 (1968).

²¹³ A. Denis and M. Gilbert, *Theor. Chim. Acta* **11**, 31 (1968).

²¹⁴ C. Giessner-Prettre and A. Pullman, *Theor. Chim. Acta* **9**, 279 (1968).

²¹⁵ H. Chojnacki and W. A. Sokalski, *J. Mol. Struct.* **15**, 263 (1973).

²¹⁶ H. Labhart, and E. C. Hermann, in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry" (E. D. Bergmann and B. Pullman, eds.), p. 76. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press), New York, 1970.

²¹⁷ A. C. Blizzard and D. P. Santry, *J. Theor. Biol.* **25**, 461 (1969).

²¹⁸ B. Mély, Ph. D. Thesis, Univ. Paris, 1968.

²¹⁹ B. Mély and A. Pullman, *Theor. Chim. Acta* **13**, 278 (1969).

²²⁰ E. Clementi, J. M. André, M. C. André, D. Klint, and D. Hahn, *Acta Phys. Acad. Sci. Hung.* **27**, 493 (1969).

²²¹ A. Pullman, *Int. J. Quant. Chem.* **2s**, 187 (1968).

²²² A. Pullman and B. Pullman, *Advan. Quant. Chem.* **4**, 267 (1968).

²²³ B. Pullman and A. Pullman, *Progr. Nucl. Acid Res. Mol. Biol.* **9**, 327 (1969).

²²⁴ A. Pullman, *Ann. N.Y. Acad. Sci.* **158**, 65 (1969).

²²⁵ B. Pullman, *Int. J. Quant. Chem.* **3s**, 83 (1969).

²²⁶ A. Pullman, in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry" (E. D. Bergmann and B. Pullman, eds.), p. 9. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1970.

²²⁷ A. Pullman, in "Sigma Molecular Orbital Theory" (O. Sinanoğlu and K. Wiberg, eds.), p. 280. Yale Univ. Press, New Haven, Connecticut, 1970.

comparison of the results obtained by different methods. Figures 3 and 4 give the net π - and ($\pi + \sigma$)-charge distributions, respectively, for form 2 of cytosine. An analysis of all the results of semiempirical and non-empirical calculations shows that they predict net negative π -charges on atoms O-7, N-3, and C-5 ($q_7 > q_3 > q_5$), but the IEHT calculations²¹¹ predict also negative net π -charges on C-2, C-4, and C-6. The IEHT method,^{228a} however, is still in an evolving stage, and its results are frequently dubious.

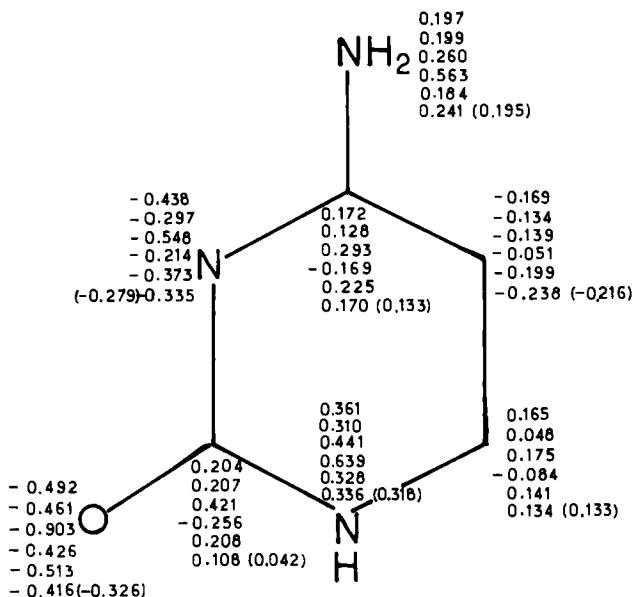


FIG. 3. Net π -charges in cytosine calculated by different methods (from top to bottom: π -HMO, π -SCF MO, EHT, IEHT, CNDO/2, nonempirical calculations). Data taken from Pullman and Pullman^{1,222,223,228} and from Clementi *et al.*²²⁰ (in parentheses).

All calculations (except the IEHT ones) predict the π -charge density on carbon C-5 to be higher than that on carbon C-6 and locate partial positive π -charges on C-2, C-4, and C-6, as well as on the amino group.

Several discrepancies occurring in the calculations made by different workers are evidently due to the different approximations involved in

²²⁸ A. Pullman, *Top. Curr. Chem.* **31**, 45 (1972).

^{228a} The IEHT method with a different set of parameters has been applied by Rein *et al.*²¹² to calculate the total charge distribution in cytosine and other nucleic acid bases (cf. Fig. 4). The π -charges have not been indicated.

the methods. In spite of these discrepancies, the methods give qualitatively similar results. The conclusions drawn from the results of calculations are highly significant for predicting the reactivity of the nucleic acid bases (see below).

Several physicochemical properties of the bases, outstanding among which is the dipole moment, depend on both the π - and σ -electrons of the molecule. Calculated total charges are indicated on Fig. 4. Those on the nitrogens are in the order N-3 > N-8 > N-1, with the exception of the nonempirical calculations giving the order N-8 > N-1 > N-3. Total

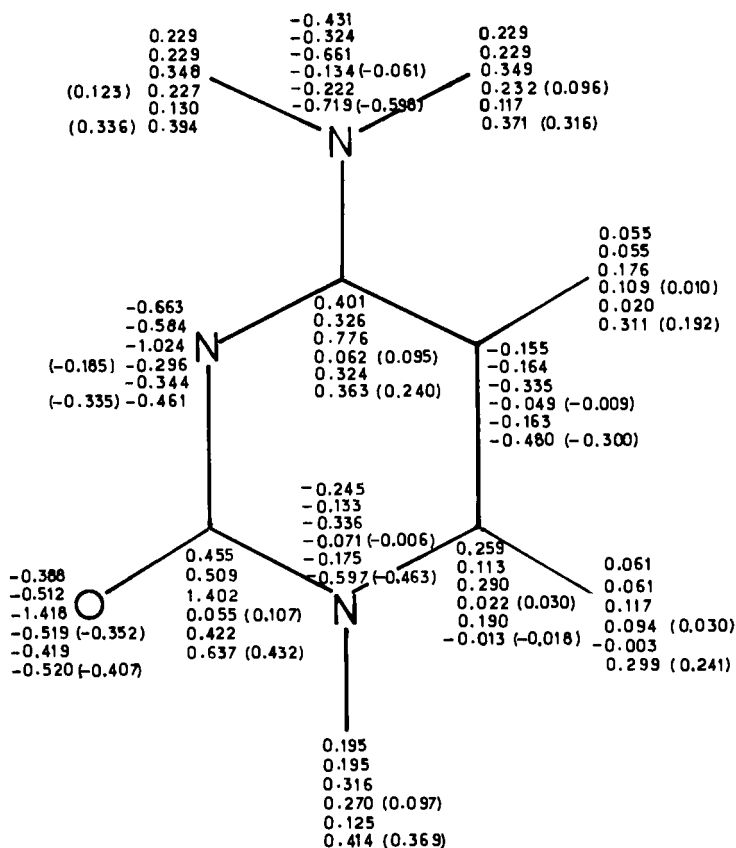


FIG. 4. Total net charges in cytosine calculated by different methods (from top to bottom: π -HMO + σ -Del Re, π -SCF MO + σ -Del Re, EHT, IEHT, CNDO/2, nonempirical calculations). Data taken from Pullman and Pullman,^{1,222,223,228} Rein *et al.*²¹² (IEHT, in parentheses), and Clementi *et al.*²²⁰ (nonempirical, in parentheses).

charges on C-5 are higher than on C-6. Similarly to the π -electronic charges, the total charges on C-2, C-4, and C-6 are partially positive.

Unfortunately, it is not possible at present to compare theoretical charge distributions with the experimental results. Although, very recently, generalized X-ray scattering factors have been used²²⁹ to estimate gross valence atomic populations in several N-heterocyclic compounds including uracil, a similar estimate for cytosine is not available.

Figures 5 and 6 give the π - and total electronic charges calculated by the CNDO/2 method for several tautomeric forms of cytosine, 5-F and 6-F-cytosine, and of N⁸-amino and N⁸-hydroxy substituted cytosines. The last two compounds as discussed before are important in the theory of mutagenesis, being products of reaction between cytosine and hydrazine or hydroxylamine, respectively.

It can be seen that the 5-F or 6-F substitutions change the π - and total electronic charges mainly at the C-5 or C-6 atoms and in their surroundings. Substitution of the amine or hydroxy group at the N-8 atom does not change significantly the charge distribution in the cytosine ring.

A more practical representation of the electron distribution in a molecule can be obtained from the probability density contour maps. Isodensity contours in the molecular plane and in a plane parallel to the molecular plane at an altitude of 0.8 atomic unit have been calculated²³⁰ for three nucleic acid bases (adenine, thymine, and cytosine) from non-empirical wave functions. The first type of contour gives an overall picture of σ -bonding in the molecule, and the second characterizes the π -electron density.

A comparison of the σ -contours in cytosine (Fig. 7a) and other nucleic acid bases²³⁰ (cf. Fig. 14a for thymine) indicates a great constancy in the individual aspect of certain bonds, atoms, or groups of atoms in different environments, e.g., the characteristic shape of the C=O or NH₂ groups. Similarly, all the NH groups display a typical triangular form. All the pyridinelike nitrogens display another triangular distribution with the directional character of the lone pair clearly visible. On the other hand, the nonbonding electrons of the carbonyl oxygens are buried inside a nearly spherical distribution.

The contours above the molecular plane (related to the π -electron densities) show neatly the differences between pyrrolic or amino-type and pyridinic nitrogens²³⁰ (Fig. 7b; cf. Fig. 14b for thymine). The

²²⁹ R. F. Stewart, *J. Chem. Phys.*, **53**, 205 (1970).

²³⁰ A. Pullman, M. Dreyfus, and B. Mély, *Theor. Chim. Acta* **17**, 85 (1970).

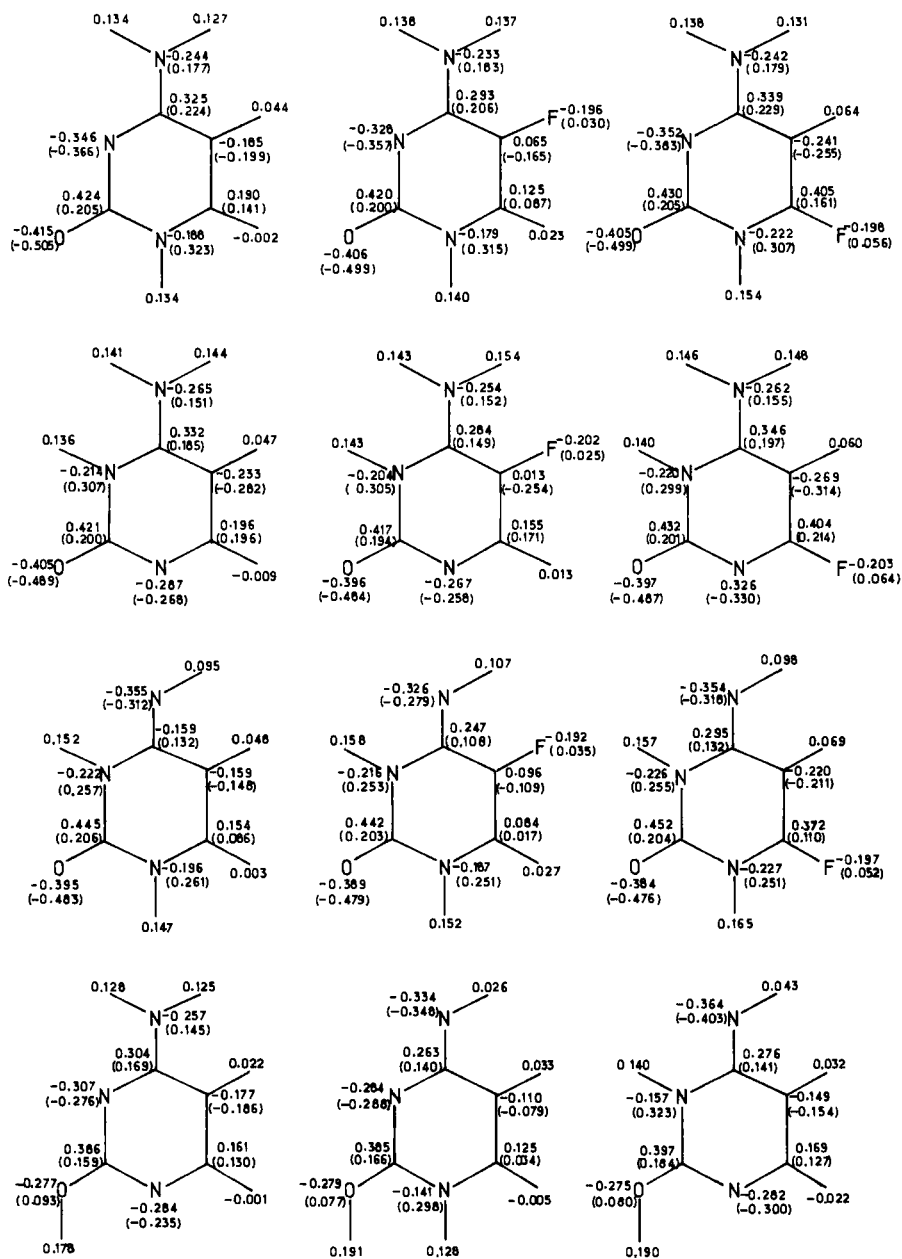


FIG. 5. Net total electronic charges in cytosine and fluorocytosine tautomers calculated by the CNDO/2 method. The numbers in parentheses indicate π -charges.

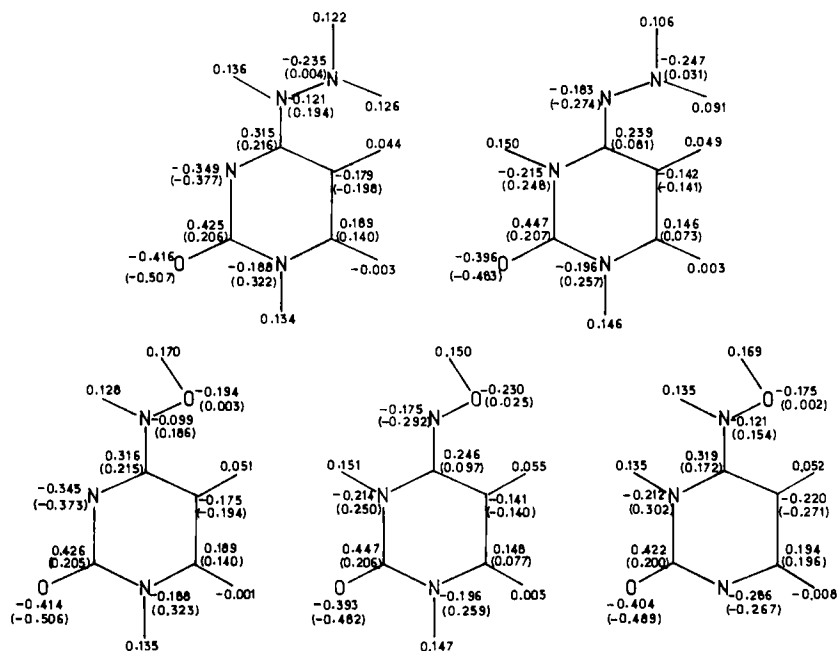


FIG. 6. Net total electronic charges in N^4 -amino and N^4 -hydroxy substituted cytosine tautomers calculated by the CNDO/2 method. The numbers in parentheses indicate π -charges.

carbon atoms of the rings appear very similar with the exception of C-6 of pyrimidine. This result confirms the strong π -polarity of this particular atom. The reader is referred to the original paper²³⁰ and reviews^{228,231} for the detailed discussion of the density contour maps.

2. Dipole Moments

The dipole moment of cytosine has been calculated many times by different methods. Until very recently, no experimental data were available on this subject. A short time ago, an attempt was undertaken at the Institute of Biochemistry and Biophysics of the Polish Academy of Sciences, Warsaw, to measure the dipole moments of cytosine, of a number of its derivatives, and of some cytidines. Table X collects the preliminary results of these measurements. As we see, the value of the dipole moment of cytosine is relatively large (> 6.0 D), probably about

²³¹ A. Pullman and B. Pullman, in "The Purines—Theory and Experiment" (E. D. Bergmann and B. Pullman, eds.), p. 1. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1972.

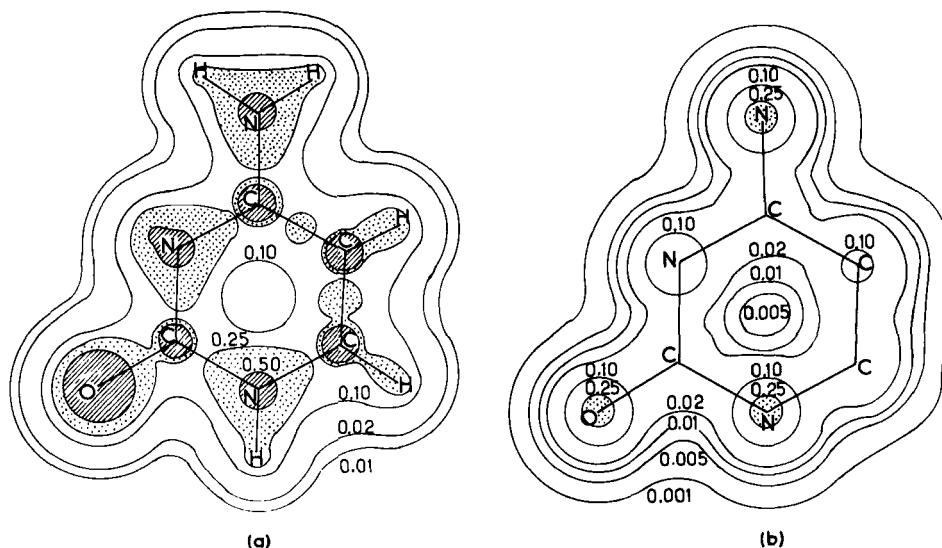


FIG. 7. Contours of constant values of electron density in the molecular plane of cytosine (a) and in a plane parallel to the molecular plane at 0.8 atomic unit from it (b).²³⁰ Values as indicated.

2 D higher than the dipole moment of uracil or thymine. All the quantum-mechanical calculations predicted a greater moment for cytosine (and guanine) than for uracil or thymine (and adenine). The agreement between the experimental dipole moment of cytosine and the values calculated by different methods is satisfactory (cf. Table XI)

TABLE X

DIPOLE MOMENTS^a OF CYTOSINES AND CYTOSINE NUCLEOSIDES (AT 25°)

Compound	Dipole moment (D)	Solution
1-Cyclohexyl-	6.1 ± 0.1	Dioxan
1-Cyclohexyl- <i>N</i> - ⁸ -methyl-	6.32 ± 0.02	Dioxan
	5.0 ^b ± 0.2	Benzene
1,5- <i>N</i> - ⁸ -trimethyl-	6.97 ± 0.01	Dioxan
	6.56 ± 0.05 ^b	Benzene
1-Ribosyl-	5.9 ± 0.1	Dioxan
1-(2',3',5'-Tri- <i>O</i> -methylribosyl)-	6.06 ± 0.02	Dioxan

^a All figures presented for cytosines are unpublished data measured by I. Kułakowska and K. L. Wierzchowski, and those for cytosine nucleosides by I. Kułakowska and A. Rabczenko (Institute of Biochemistry and Biophysics, Polish Academy of Science, Warsaw).

^b Uncertain value.

provided that dipole moments calculated by EHT or IEHT are neglected, being always much higher than the experimental values. Moreover, the exact comparison of the calculated moments with the experimental value is difficult in the case of cytosine because of the uncertainty in the experimental value. It must also be remembered that in all the calculations (Tables XI and XII) the planarity of the molecule was assumed. In fact, the calculated dipole moments of amino compounds with the amino group lying in plane or out of plane of the molecule are significantly different (see, e.g., ref. 232). A very recent CNDO/2 study¹⁵⁶ of cytosine dipole moments has shown that it was significantly decreased (to about 7.2 D) when the NH_2 group was out of plane.

From past experience,³ the direction of the calculated dipole moment of cytosine (see Tables XI and XII) is reliable.

3. *Molecular Isopotential Maps—Chemical Reactivity*

The study of the reactivity of the nucleic acid bases utilizes indices based on the knowledge of the molecular electronic structure. There are two possible approaches to the prediction of the chemical properties of a molecule, the isolated and reacting-molecule models (or "static" and "dynamic" ones, respectively). Frequently, at least in the older publications, the chemical reactivity indices for heteroaromatic compounds were calculated in the π -electron approximation, but in principle there is no difficulty to define similar quantities in the all-valence or all-electron methods. The subject is a very broad one, and we shall here mention only a new approach to chemical reactivity based on non-empirical calculations, namely the so-called molecular isopotential maps.

The electrostatic potential $V(r_i)$ at a given point i created in the neighboring space by the nuclear charges and the electronic distribution of a molecule can be calculated from the molecular wave function (strictly speaking from the corresponding first-order density function). As this quantity is directly obtainable from the wave function, it does not suffer from the drawbacks inherent in the classical population analysis.

²³² J. E. Bloor and D. J. Breen, *J. Phys. Chem.* **72**, 716 (1968).

²³³ H. DeVoe and I. Tinoco, *J. Mol. Biol.* **4**, 500 (1972).

²³⁴ H. Berthod and A. Pullman, *C.R. Acad. Sci.* **259**, 2711 (1964).

²³⁵ H. Berthod, C. Giessner-Prettre, and A. Pullman, *Theor. Chim. Acta* **5**, 53 (1966).

²³⁶ S. Kang, *J. Mol. Biol.* **58**, 297 (1971).

TABLE XI
DIPOLE MOMENTS OF CYTOSINES^a CALCULATED BY DIFFERENT METHODS^b

Method	References	Tautomer of cytosine	Dipole moment ^c		
			$\mu_n(\alpha_n)^d$	$\mu_\sigma(\alpha_\sigma)^e$	$\mu_{tot}(\alpha_{tot})^f$
π -HMO ^b	233	2, 1-CH ₃ -	6.9 (118)	1.7 (63)	8.0 (108)
π -SC HMO (ω -technique)	169 ^g	2	3.91 (92)		5.55 (86)
π -HMO +	234, 145 ^g	2	5.5 (97)	1.6 (95)	7.0 (96)
σ -Del Re	146 ^g	2, 1-CH ₃ -	5.29 (96)	1.85 (99)	7.14 (97)
π -SCF MO +	235, 226	2	5.4 (113)	1.7 (99)	7.1 (110)
σ -Del Re	208	2, 1-CH ₃ -	5.4 (112)	1.9 (99)	7.2 (109)
	144	6, 1,3-diCH ₃ -			5.22
EHT	224, 229	2			16.5 (109)
	223	2			*17.3 (106)
IEHT	211	2	8.12 (127.4)	2.39 (106.0)	*12.43 (124.6)
				3.48 (90.0) ^h	
	224	2			*12.9 (121)
	212	2			6.69 ⁱ

CNDO/2 ^f	214	2	6.39 (108)	1.78 (− 89) 3.17 (84) ^h	*7.61 (102)
CNDO/2—Jaffé ^k	150	2			5.66 *8.27
<i>Ab initio</i>	219, 226 220	2 2	1.29 (68)	5.76 (111)	6.76 (103) 6.4

^a Dipole moment of cytidine as a function of rotation about the glycosidic bond has been calculated by the INDO method by Kang²³⁶ (for the different puckerings of the sugar, $\Phi_{C(4')-C(5')} = 60^\circ$ and 300°) and by the PCILO method by Weiler-Feilchenfeld *et al.*²³⁷ (for the C₃-endo gg conformation). Berthod and Pullman²³⁸ using the PCILO method have calculated the dipole moments of anti and syn conformers of cytidine (C₃-endo gg) to be equal to 8.8 and 6.7 D, respectively, and those of deoxycytidine (C₂-endo gg) to be equal to 10.0 and 4.1 D, respectively. For the π -SCF MO dipole moment of cytosine see refs^{104,174,177,178}.

^b Cf. the reviews 1, 222–228.

^c Dipole moment in Debye units; the angles (in degrees) with the axis N(1)–C(4) (measured counterclockwise) are given in parentheses.

^d π -Component of the dipole moment.

^e σ -Component of the dipole moment (hybridization moment not included).

^f Total dipole moment (hybridization moment included (*) or not included).

^g Dipole moment of guanine-cytosine base pair has also been calculated.

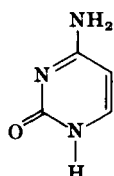
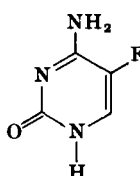
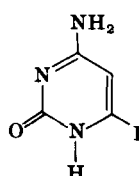
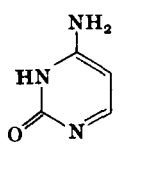
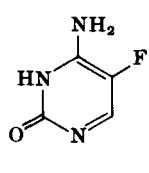
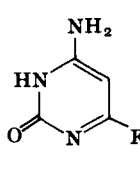
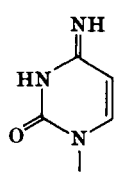
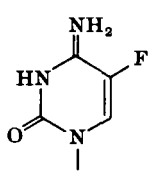
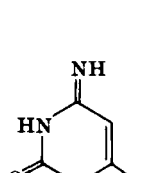
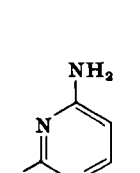
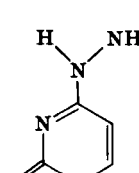
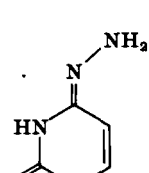
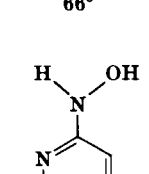
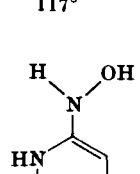
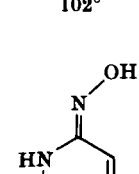
^h Hybridization moment.

ⁱ Including dipole moment of lone pairs.

^j See Table XII for the dipole moments of different tautomers of cytosine and its derivatives as calculated in the present paper. For other CNDO/2 calculations on dipole moment of cytosine, see refs. 153, 215, 239.

^k CNDO/2 method modified by Del Bene and Jaffé.^{240,241}

TABLE XII
CNDO/2 DIPOLE MOMENTS OF CYTOSINE AND ITS DERIVATIVES^a

			
7.70 D 101°	5.76 D 100°	6.48 D 110°	8.64 D 146°
			
7.14 D 156°	9.47 D 152°	5.21 D 68°	3.89 D 52°
			
3.50 D 66°	3.13 D 117°	7.87 D 102°	5.01 D 69°
			
6.11 D 112°	9.32 D 158°	3.06 D 64°	

^a The angles are measured anti-clockwise with respect to the axis N(1)-C(4).

Bonaccorsi *et al.*^{242,243} have suggested an appropriate index for the study of chemical reactivity. The interaction energy between the molecular distribution (unperturbed) and an external point charge q placed at point i is $qV(r_i)$. This quantity is rigorously the first-order perturbation energy of the molecule in the field of the charge q . Taking q as a unit positive charge the interaction potential can be used for studying proton affinities (basicities) and in principle other electrophilic attacks.

The study of the nucleic acid bases is interesting because they possess many possible sites of protonation or electrophilic attack. Isopotential maps have been constructed for adenine, cytosine, and thymine.²⁴⁴ They may be used to study theoretically the proton affinities of the different atoms in these molecules. It is well known that protonation of cytosine, its nucleotide or nucleoside, occurs at N-3^{94,245-247} (cf. Section II); alkylation also occurs at N-3.^{103,248,249} Nevertheless protonation of the oxygen of cytosine in DNA has been reported.²⁵⁰ The basic pK of cytosine is higher than that of adenine. The isopotential map in the molecular plane of cytosine (Fig. 8) shows that the potential well is deeper for N-3 than for O and the minimum for N-3 in cytosine is deeper than for any nitrogen in adenine. These maps, and their confrontation with the experimental facts have been discussed^{228,244}

²³⁷ H. Weiler-Felchenfeld, G. Zvilichovsky, E. D. Bergmann, B. Pullman, and H. Berthod, in "Conformation of Biological Molecules and Polymers" (E. D. Bergmann and B. Pullman, eds.), p. 311. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1973.

²³⁸ H. Berthod and B. Pullman, *Biochem. Biophys. Res. Commun.* **46**, 125 (1972).

²³⁹ N. V. Zheltovsky and V. I. Danilov, "Quantum Mechanical Study of the Electronic Structure of the Nucleic Acids Bases by CNDO/2 Method." Preprint Inst. Phys. Acad. Sci. Ukr. SSR, Kiev, 1973.

²⁴⁰ J. Del Bene and H. H. Jaffé, *J. Chem. Phys.* **48**, 1807 (1968).

²⁴¹ J. Del Bene and H. H. Jaffé, *J. Chem. Phys.* **48**, 4050 (1968).

²⁴² R. Bonaccorsi, C. Petrongolo, E. Scrocco, and J. Tomasi, in "Quantum Aspects of Heterocyclic Compounds in Chemistry and Biochemistry" (E. D. Bergmann and B. Pullman, eds.), p. 181. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1970.

²⁴³ R. Bonaccorsi, E. Scrocco, and J. Tomasi, *J. Chem. Phys.* **52**, 5270 (1970).

²⁴⁴ R. Bonaccorsi, A. Pullman, E. Scrocco, and J. Tomasi, *Theor. Chim. Acta* **24**, 51 (1972).

²⁴⁵ L. F. Cavalieri and B. H. Rosenberg, *J. Amer. Chem. Soc.* **79**, 5352 (1957).

²⁴⁶ G. Zubay, *Biochim. Biophys. Acta* **28**, 644 (1958).

²⁴⁷ R. M. Izatt, J. J. Christensen, and J. H. Rytting, *Chem. Rev.* **71**, 439 (1971).

²⁴⁸ P. Brookes and P. D. Lawley, *Biochim. Biophys. Acta* **26**, 450 (1957).

²⁴⁹ P. D. Lawley, *Progr. Nucl. Acid. Res. Mol. Biol.* **5**, 89 (1966).

²⁵⁰ N. F. Dove, F. A. Wallace, and N. Davidson, *Biochim. Biophys. Res. Comm.* **1**, 312 (1959).

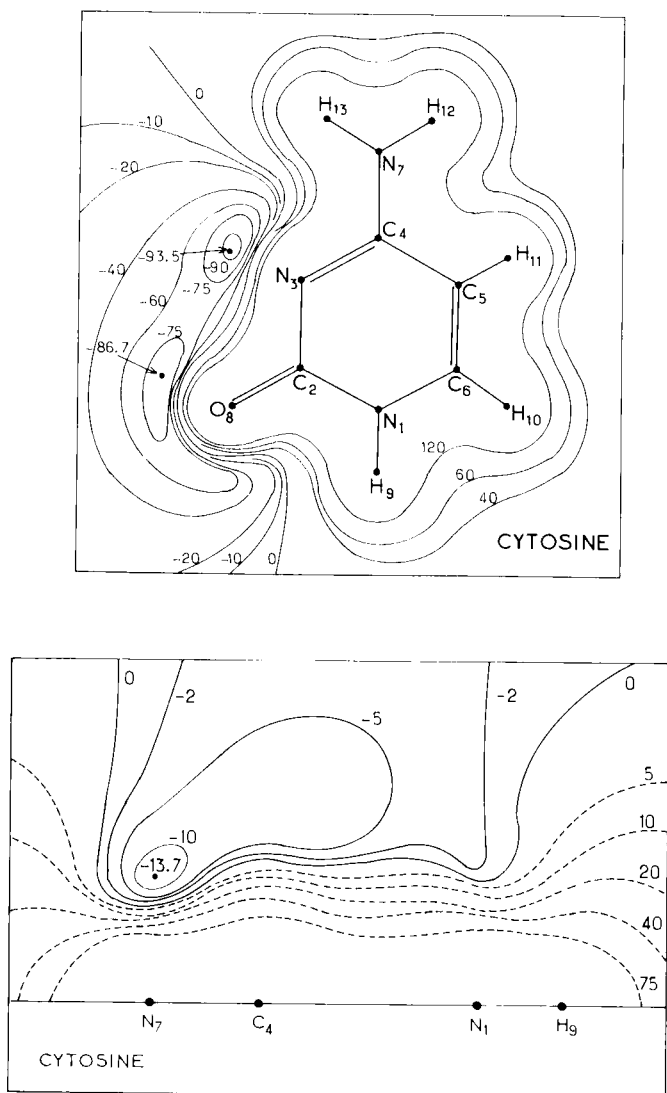


FIG. 8. Electrostatic molecular potential-energy maps for cytosine in the ring plane (top) and in the plane perpendicular to the ring plane and passing through atoms as indicated (bottom).²⁴⁴

(for isopotential maps for adenine and guanine calculated from CNDO/2 wave functions, see ref. 251).

Very recently Port and Pullman²⁵² have made a theoretical study of the effect of the water environment on the structure of adenine, guanine, thymine, and cytosine. They calculated the electrostatic component of the interaction energy between the bases and water molecules. This part of the interaction energy plays the dominant role in hydrogen bonding and particularly in determining the relative orientations of the two partners at their equilibrium distance. The calculation of the interaction energy requires a knowledge of the wave function for the base and for water. The nonempirical wave functions were taken from previous calculations on the nucleic acid bases²²⁰ and on water (unpublished results of H. Berthod and A. Pullman). The water molecule was allowed to turn completely around the periphery of the base, a constant distance of 2.85 Å being maintained between the oxygen of water and the atoms of the base. The calculations show (Fig. 9) that the

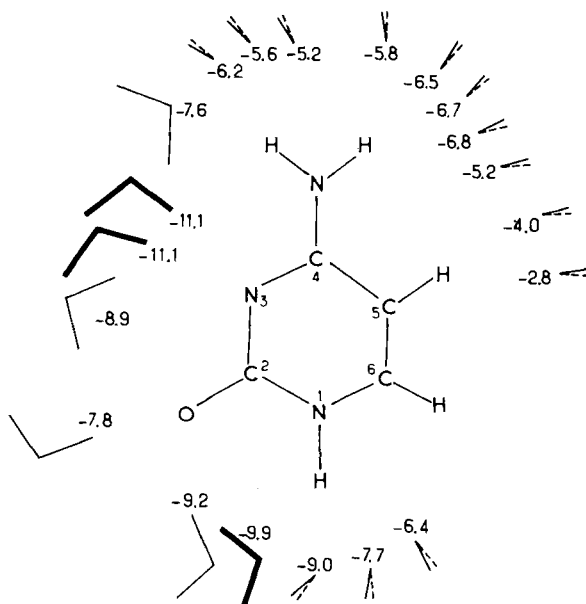


FIG. 9. Hydration sites in cytosine.²⁵² Energies given in kilocalories per mole. Heavy lines, preferred hydration sites; full lines, coplanar arrangement of water and base; half-dashed, perpendicular arrangement of water with respect to the plane of the base.

²⁵¹ C. Giessner-Prettre and A. Pullman, *C.R. Acad. Sci., Ser. C* **272**, 750 (1971).

²⁵² G. N. J. Port and A. Pullman, *FEBS Lett.* **31**, 70 (1973).

N-3 atom was the most favorable hydration site in cytosine. A second hydration site is situated on the other side of the carbonyl group, between the oxygen and the hydrogen at N-1. There are no other regions of comparably strong attraction in cytosine. It is worth noting that the in-plane interactions are much more favorable than the out-of-plane ones. This has been illustrated²⁵² by calculations for a water molecule placed above the NH_2 group of cytosine (or adenine).

E. MOLECULAR ORBITAL ENERGIES: ELECTRON-DONATING ELECTRON-ACCEPTING PROPERTIES

A knowledge of the ionization potentials and electron affinities of the nucleic acid bases, or in general the understanding of the electron donor or acceptor properties of the bases, is important for the appreciation of charge transfer complexations and, together with the knowledge of the dipole moments of the bases, has a fundamental significance for the elucidation and evaluation of the intermolecular forces that govern the interaction of the bases with each other or with exogenous substances.

The values of the ionization potentials of the bases were unknown experimentally until quite recently, and the electron affinities are still unknown. The first experimental determination of the ionization potentials of the pyrimidine bases (uracil, thymine), by Akopyan and Vilesov,²⁵³ dates from 1965. Two years later Bergmann *et al.*²⁵⁴ measured the ionization potentials of some purine and pyrimidine bases including cytosine. The cytosine ionization potential as determined by mass spectrometry²⁵⁴ was found to be 8.90 ± 0.2 eV. On the other hand the potential determined from the "charge transfer" spectra by Fulton and Lyons²⁵⁵ was 7.98 eV.

The simplest method for calculating the ionization potentials and the electron affinities is the π -HMO method. Such an evaluation is particularly suitable for the determination of the relative electron donor-acceptor properties of the molecules. The appropriate indices are the energies of the highest occupied molecular orbitals (HOMO) for the electron donor capacity and the energies of the lowest empty molecular orbitals (LEMO) for the electron acceptor abilities. These simple theoretical predictions gave an excellent interpretation^{1,256} of the

²⁵³ M. E. Akopyan and F. I. Vilesov, *Dokl. Akad. Nauk SSSR* **161**, 1110 (1965).

²⁵⁴ C. Lifschitz, E. D. Bergmann, and B. Pullman, *Tetrahedron Lett.*, 4583 (1967).

²⁵⁵ H. Fulton and L. E. Lyons, *Aust. J. Chem.* **21**, 419 (1968).

²⁵⁶ A. Pullman and B. Pullman, in "Quantum Theory of Atoms, Molecules, Solid State" (P. O. Löwdin, ed.), p. 345. Academic Press, New York, 1966.

electrochemical behavior of these biomolecules, including polarographic oxidizability and reducibility of the bases. For about ten years the theoretical values usefully replaced the lacking experimental ones in the study of a number of problems.

Table XIII collects the ionization potentials and electron affinities

TABLE XIII
THE CALCULATED π -SCF MO IONIZATION POTENTIALS AND
ELECTRON AFFINITIES OF CYTOSINE^a

References	Compound	I^b (eV)	A^b (eV)
257 ^c	2	8.3 9.8 ^d _{n(O-7)} 11.0 ^d _{n(N-3)}	
235 ^c	2	8.16	-0.87
208 ^c	2,1-CH ₃ -	7.97	-0.82
	3,3-CH ₃ -	7.60	-0.26
	2,5-CH ₃ -	8.00	-0.89
	2,N-8-diCH ₃ -	7.93	-0.80
258	2	8.41 ^e	-0.24 ^e
	1	8.08 ^e	-1.25 ^e
	3	8.12 ^e	-0.24 ^e
149	2	9.25 9.68 ^f	1.17
	6	10.61 10.15 ^f	1.20

^a The following papers may be consulted for the ionization potentials and electron affinities of cytosine and of its complexes with different partners: cytosine,^{171,173,177,178,180,184,186,200,201,203,207,259,260} guanine-cytosine,^{171,182-184,186} 2-NH₂-purine (amine form)-cytosine, 2-NH₂-purine(imine form)-cytosine and 2-NH₂-purine(amine form)-cytosine (form 6),¹⁸⁰ cytosine-cytosine and cytosine-cytosine-cytosine.¹⁷¹

^b Ionization potential (I) and electron affinity (A) were calculated from Koopmans' theorem, except those indicated.

^c Using the corrected π -SCF MO procedure (an empirical diminution of the values of the atomic valence-state ionization potentials).

^d The lone-pair ionization potentials calculated according to Nakajima and Pullman.²⁸¹

^e Corrected values (the energies of molecular orbitals were decreased by a constant value).

^f Calculated by the "half-electron" method of Dewar *et al.*²⁶² These I -values correspond to the adiabatic ionization potential.

²⁵⁷ A. Pullman and M. Rossi, *Biochim. Biophys. Acta* **88**, 211 (1964).

²⁵⁸ T. L. Kunii and H. Kuroda, *Theor. Chim. Acta* **11**, 97 (1968).

²⁵⁹ R. K. Nesbet, *Biopolym. Symp.* **1**, 129 (1964).

²⁶⁰ S. Fraga and C. Valdemoro, Technical Report TC-6703, Dep. Chem., Univ. of Alberta (1967).

²⁶¹ T. Nakajima and A. Pullman, *J. Chim. Phys.*, 793 (1958).

²⁶² M. J. S. Dewar, J. A. Hashmall, and G. G. Venier, *J. Amer. Chem. Soc.* **90**, 1953 (1968).

for cytosine and some of its derivatives calculated by means of the π -SCF MO method in a few representative papers.

The π -SCF MO procedure, within the Pariser-Parr approximation using the ionization potentials of the atomic valence-states, yields values of molecular ionization potentials that are in general too high, sometimes by as much as 2 eV, with respect to experimental values. In order to have a better value, two approaches are generally employed. According to the first one, the ionization potential of a molecule is calculated with respect to a reference compound (e.g., benzene) as the negative of the energy of the highest occupied molecular orbital diminished by the difference between the negative value of the highest occupied molecular orbital of the reference molecule and its experimental ionization potential. The second approach utilizes an appropriately corrected π -SCF MO method, in which the effect of atomic reorganization energy upon bond formation is taken into account by an empirical decrease of the values of the atomic valence-state ionization potentials. The procedure reproduces correctly the experimental values of the molecular ionization potentials of a number of fundamental compounds. It can be seen from Table XIII that the numerical values of the predicted potentials vary from one calculation to another. The relative order of the predicted potentials of the nucleic acid bases, however, is generally similar in all methods including the all-valence or all-electron ones and also similar to the order predicted originally by the π -HMO calculations. The "corrected" ionization potential of cytosine as determined by Pullman and Rossi,²⁵⁷ and Kunii and Kuroda,²⁵⁸ are in good agreement with the experimental data (8.0–8.9 eV). Pullman and Rossi²⁵⁷ have attempted to evaluate also the nitrogen and oxygen lone-pair ionization potentials of the bases. Using a previously given expression²⁶¹ for the lone-pair ionization potentials they have evaluated the relative values of these potentials with respect to those of the π -electrons. In cytosine the order of increasing ionization potentials is $\pi < n(O) < n(N)$. As for the comparison among the nucleic acid bases, the predicted values of the ionization potentials indicated that cytosine is the best $n(N)$ -donor and a better $n(O)$ -donor than uracil.²⁵⁷ It should also be added that all the quantum-mechanical calculations indicate that the purines are better π -donors than the pyrimidines.

All-valence and all-electron methods (except IEHT) predict that the first ionization potential of cytosine and of several derivatives of a cytosine is of the π -type (Tables XIV and XV). An ionization potential of the π -type is the first one in all tautomers of cytosine. Similarly, the electron affinities in all cytosine tautomers should be of the π -type.

The energies of the molecular orbitals of the guanine-cytosine base

TABLE XIV

ENERGIES OF THE LOWEST EMPTY (LEMO) AND THREE HIGHEST OCCUPIED (HOMO) MOLECULAR ORBITALS^a IN CYTOSINES CALCULATED BY CNDO/2 METHOD

Compound, tautomer	LEMO (eV)	HOMO (eV)		
Cytosine, 2	2.85	-10.79	-11.82 σ	-13.30
5-F-cytosine, 2	2.30	-10.98	-12.19 σ	-13.33
6-F-cytosine, 2	2.61	-11.12	-12.34 σ	-13.72
N ⁴ -Aminocytosine, 2	2.86	-10.71	-11.78 σ	-12.25
N ⁴ -Hydroxycytosine, 2	2.75	-10.85	-11.90 σ	-12.79
Cytosine, 1	4.05	-11.56	-11.76 σ	-13.12
Cytosine, 3	2.87	-10.48	-11.93 σ	-14.05 σ
5-F-cytosine, 3	2.29	-10.50	-12.31 σ	-14.57 σ
6-F-cytosine, 3	2.63	-10.97	-12.54 σ	-14.13 σ
N ⁴ -Hydroxycytosine, 3	2.81	-10.46	-11.97 σ	-13.89
Cytosine, ^b 4	3.21	-9.73	-11.27 σ	-14.49
Cytosine, ^b 5	2.61	-9.89	-11.93 σ	-13.99 σ
Cytosine, 6	3.05	-11.26	-12.66	-12.68 σ
5-F-cytosine, 6	2.63	-11.32	-12.89	-12.99 σ
6-F-cytosine, 6	2.82	-11.49	-13.05	-13.15 σ
N ⁴ -Aminocytosine, 6	3.03	-10.24	-12.54	-12.77 σ
N ⁴ -Hydroxycytosine, 6	2.94	-10.73	-12.50 σ	-12.68

^a Unlabeled orbitals are π levels.

^b Data taken from Ref. 156.

pair have also been calculated in several papers using different methods.^{262a} For the energies of the highest occupied molecular orbital and the lowest empty one of the base pairs calculated by means of the π -HMO method see refs. 1, 140, 171, 263. All calculations show that the molecular levels of the pairs correspond to slightly perturbed levels of the parent bases. The highest occupied molecular orbital of the pair originates from the corresponding molecular orbital of guanine, while the second highest occupied orbital of the pair originates from the HOMO of cytosine. Thus the electron-donor properties of the guanine-cytosine pair depend on the electron-donor properties of guanine (perturbed by cytosine). On the other hand, the lowest empty molecular orbital of the guanine-cytosine pair, and the next one, correlate with the lowest empty molecular orbitals of cytosine and guanine, respectively. The electron-acceptor properties of the guanine-cytosine base

^{262a} See ref. 190 for the π -SCF MO ionization potential and electron affinity of the hydrogen-bonding pairs of cytosine-2-NH₂-purine (amine form), cytosine-2-NH₂-purine (imine form), and cytosine (form **6**)-2-NH₂-purine (amine form).

²⁶³ A. Pullman, *C.R. Acad. Sci.* **258**, 5435 (1963).

TABLE XV
ENERGIES OF THE LOWEST EMPTY (LEMO) AND THREE HIGHEST (HOMO) MOLECULAR ORBITALS OF CYTOSINE
CALCULATED BY DIFFERENT ALL-VALENCE OR ALL-ELECTRON METHODS

Method	EHT	IEHT	CNDO/2			<i>Ab initio</i>	
References	224	212	211	214	<i>a</i>	220	218, 219
LEMO (eV)	—	− 7.54 π	—	—	2.85 π	—	+ 2.20 π
HOMO (eV)	− 12.50 π	− 8.55 ^b σ	− 9.07 σ	− 10.78 π	− 10.79 π	− 9.83	− 9.79 π
	− 12.58 σ	− 9.12 π	− 10.39 π	− 11.81 σ	− 11.82 σ	− 11.91	− 11.40 ^b σ
	− 13.51 π	− 9.61 ^c σ	− 10.54 π	− 13.21 π	− 13.30 π	− 12.04	− 11.45 π

^a Present calculations.

^b Mainly localized on oxygen.

^c Mainly localized on N-3.

pair are thus related essentially to these properties in cytosine (perturbed by guanine). The correlation between the molecular orbitals of the bases and those of the base pair has been confirmed by recent CNDO/2 calculations on the guanine-cytosine pair.²¹⁷

It should also be added that the reminimization of the wave functions (on going from the closed-shell to open-shell treatment) leads to an insignificant fall in energy of the ions of the base pair (see Danilov *et al.*^{184,209}). A similar situation occurs in the calculations on isolated nucleic acid bases.^{173,177,184,203} Comparing the ionization potentials and electron affinities of the pair with those of the component bases (see Table XVI and Blizzard and Santry²¹⁷), it is seen that the donor and acceptor properties of the guanine-cytosine pair are stronger than those of guanine and cytosine. A very recent nonempirical calculation by Clementi *et al.*²⁶⁴ on the guanine-cytosine pair has also predicted the ionization potential of the pair to be lower than that of guanine or

TABLE XVI

THE ENERGIES OF HIGHEST OCCUPIED (HOMO) AND LOWEST EMPTY (LEMO) MOLECULAR ORBITALS OF GUANINE, CYTOSINE, AND THEIR PAIR CALCULATED BY π -SCF MO (CLOSED-SHELL)^a

References	Guanine ^b	Guanine-cytosine ^b	Cytosine ^b
182	LEMO (eV) - 1.48	- 1.86	
		- 2.61	- 2.09
	HOMO (eV) - 10.24	- 9.04	
		- 10.32	- 11.04
183 ^c	LEMO (eV)	- 0.87, - 0.54	—
		- 2.75, - 2.17	—
	HOMO (eV)	- 8.20, - 8.75	—
		- 10.77, - 11.84	—
184, 209	LEMO (eV) - 1.48 (+ 1.71)	- 1.21	
		- 2.30 (+ 2.55)	- 2.13 (+ 2.35)
	HOMO (eV) - 9.03 (+ 8.95)	- 8.83 (+ 8.73)	
		- 10.27	- 9.95 (+ 9.57)
186	LEMO (eV) - 0.04	- 0.09	
		- 1.52	- 1.34
	HOMO (eV) - 9.55	- 9.59	
		- 11.39	- 11.06

^a Except those indicated.

^b The values of the ionization potentials and electron affinities calculated by the open-shell method are given in parentheses.

^c The two sets of calculations differ in the approximations used in the method.

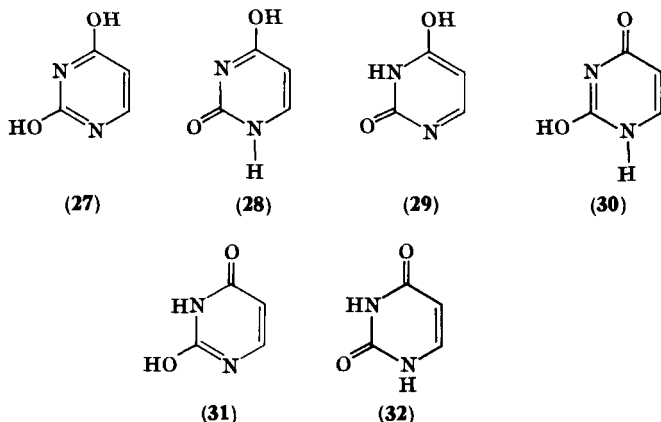
²⁶⁴ E. Clementi, J. Mehl, and W. Von Niesson, *J. Chem. Phys.* **54**, 508 (1971).

cytosine. The first ionization potential of the base pair has been predicted²⁶⁴ to be of the π -type, and (by the π -SCF MO method) to be within the range of 8.2–9.6 eV. The CNDO/2 method²¹⁷ yields the value of about 8.5 eV, and nonempirical calculations²⁶⁴ give a value lower than 8.16 eV.^{264a}

IV. Tautomerism of Uracil and Thymine

A. THE BASIC SKELETON

Like cytosine, uracil (or thymine, its 5-methyl derivative) can exist in six tautomeric forms: **27–32**. A large amount of experimental evidence shows that uracil and thymine have the diketo (dilactam)



structure **32**. This form was found in the *X-ray crystallographic studies* of uracil^{265,266} and thymine,^{267,268} of derivatives of these molecules,^{269–279} as well as of the complexes of uracils and thymines with *p*-benzoquinone,²⁸⁰ cytosines,^{18,19} or purine.^{281–294} This structure was also

^{264a} In two papers,^{217,264} the energies of the molecular orbitals of the guanine-cytosine pair have not been given. The evaluation could be made only from the correlation diagram of the molecular orbitals.

²⁶⁵ G. S. Parry, *Acta Crystallogr.* **7**, 313 (1954).

²⁶⁶ R. F. Stewart and L. H. Jensen, *Acta Crystallogr.* **23**, 1102 (1967).

²⁶⁷ K. Ozeki, N. Sakabe, and J. Tanaka, *Acta Crystallogr. Sect. B* **25**, 1038 (1969).

²⁶⁸ R. Gerdil, *Acta Crystallogr.* **14**, 333 (1961).

²⁶⁹ D. W. Green, F. S. Mathews, and A. Rich, *J. Biol. Chem.* **237**, 3573 (1962).

²⁷⁰ K. Hoogsteen, *Acta Crystallogr.* **16**, 28 (1963).

²⁷¹ G. N. Reeke and R. E. Marsh, *Acta Crystallogr.* **20**, 703 (1966).

²⁷² B. M. Craven, *Acta Crystallogr.* **23**, 376 (1967).

found in uridines and deoxyuridines,²⁹⁵⁻³¹¹ thymines,³¹²⁻³¹⁴ in dinucleosides: uridylyl-(3',5')-adenosine hemihydrate³¹⁵ and uridylyl-(3',5')-adenosine phosphate,³¹⁶ in the complexes of thymine riboside with adenosine,³¹⁷ of uridines with purines^{318,319} or adenosines^{294,320} and in uracil-mercury(II) chloride.³²¹ A very recent *neutron diffraction study* of the 1:1 complex between 9-methyladenine and 1-methylthymine³²² showed that this last compound had the form **32**. In all

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- ²⁷³ H. Mizuno, N. Nakanishi, T. Fujiwara, K. Tomita, T. Tsukihara, T. Ashida, and M. Kakudo, *Biochem. Biophys. Res. Commun.* **41**, 1161 (1970).
²⁷⁴ E. Shefter, *J. Chem. Soc. B*, 903 (1970).
²⁷⁵ H. Mizuno, T. Fujiwara, and K. Tomita, *Bull. Chem. Soc. Jap.* **45**, 905 (1972).
²⁷⁶ T. Tsukihara, T. Ashida, and M. Kokudo, *Bull. Chem. Soc. Jap.* **45**, 909 (1972).
²⁷⁷ R. Destro and R. E. Marsh, *Acta Crystallogr. Sect. B* **28**, 2971 (1972).
²⁷⁸ M. Sundaralingam, *J. Amer. Chem. Soc.* **95**, 2333 (1973).
²⁷⁹ P. Singh and D. J. Hodgson, *J. Chem. Soc., Chem. Commun.*, 439 (1973).
²⁸⁰ K. Hoogsteen, *Acta Crystallogr.* **16**, 907 (1963).
²⁸¹ F. S. Mathews and A. Rich, *J. Mol. Biol.* **8**, 89 (1964).
²⁸² L. Katz, K. Tomita, and A. Rich, *J. Mol. Biol.* **13**, 340 (1965).
²⁸³ A. E. V. Haschemeyer and H. M. Sobell, *Acta Crystallogr.* **18**, 525 (1965).
²⁸⁴ L. Katz, K. Tomita, and A. Rich, *Acta Crystallogr.* **21**, 754 (1966).
²⁸⁵ H. M. Sobell, *J. Mol. Biol.* **18**, 1 (1966).
²⁸⁶ Y. G. Baklagine, M. V. Volkenstein, and Y. D. Kondrashev, *Zh. Strukt. Khim.* **7**, 399 (1966).
²⁸⁷ S.-H. Kim and A. Rich, *Science* **158**, 1046 (1967).
²⁸⁸ K. Tomita, L. Katz, and A. Rich, *J. Mol. Biol.* **30**, 545 (1967).
²⁸⁹ S. S. Tavale, T. D. Sakore, and H. M. Sobell, *J. Mol. Biol.* **43**, 375 (1969).
²⁹⁰ F. Mazza, H. M. Sobell, and G. Kartha, *J. Mol. Biol.* **43**, 407 (1969).
²⁹¹ G. Simundza, T. D. Sakore, and H. M. Sobell, *J. Mol. Biol.* **48**, 263 (1970).
²⁹² T. Sakurai and M. Okunuki, *Acta Crystallogr. Sect. B* **27**, 1445 (1971).
²⁹³ R. Chandros, S.-H. Kim, and A. Rich, in preparation (quoted by Sobell²⁹⁴).
²⁹⁴ H. M. Sobell, in "The Purines—Theory and Experiment" (E. D. Bergmann and B. Pullman, eds.), p. 124. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1972.
²⁹⁵ D. R. Harris and W. M. MacIntyre, *Biophys. J.* **4**, 203 (1964).
²⁹⁶ E. Shefter and K. N. Trueblood, *Acta Crystallogr.* **18**, 1067 (1965).
²⁹⁷ N. Cammerman and J. Trotter, *Acta Crystallogr.* **18**, 203 (1965).
²⁹⁸ J. Iball, C. H. Morgan, and H. R. Wilson, *Nature (London)* **209**, 1230 (1966).
²⁹⁹ J. Iball, C. H. Morgan, and H. R. Wilson, *Proc. Roy. Soc. Ser. A* **295**, 320 (1967).
³⁰⁰ E. Shefter, M. P. Kotick, and T. J. Bardos, *J. Pharm. Sci.* **56**, 1293 (1967).
³⁰¹ M. A. Viswamitra, B. S. Reddy, M. N. G. James, and G. J. B. Williams, *Acta Crystallogr. Sect. B* **28**, 1108 (1972).
³⁰² C. L. Coulter, *Acta Crystallogr. Sect. B* **25**, 2055 (1969).
³⁰³ E. Shefter, M. Barlow, R. A. Sparks, and K. N. Trueblood, *Acta Crystallogr. Sect. B* **25**, 895 (1969).
³⁰⁴ A. Rahman and H. R. Wilson, *Acta Crystallogr. Sect. B* **26**, 1765 (1970).
³⁰⁵ S. W. Hawkinson and C. L. Coulter, *Acta Crystallogr. Sect. B* **27**, 34 (1971).
³⁰⁶ A. Rahman and H. R. Wilson, *Acta Crystallogr. Sect. B* **28**, 2260 (1972).

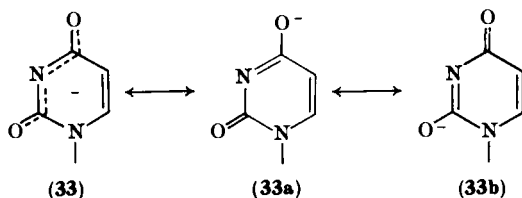
these structures the lengths of C-O bonds of the uracil rings are 1.2–1.25 Å corresponding to a very high double bond character. For the ionic forms of uracil, the X-ray crystallographic study shows that protonation of 1-methyluracil occurs at O-8.³²³

Analysis of the *IR spectra* of uracil, thymine, their nucleotides and nucleosides, confirms the predominance of structure **32** in the solid state as well as in solution.^{40,41,43,50–52,324–326} Miles,^{42,44} for instance, has found that the spectra of uracil and thymine with the N-1 and/or N-3 atoms substituted by a sugar residue or a methyl group were virtually identical to each other in the carbonyl region, but quite different from the spectrum of a corresponding enol ether. Strong supporting evidence for this structure of uracil derivatives came also from the examination of the IR spectra in the double-bond region. Uracil and thymine show two strong bonds in this region, assigned to the 2- and 4-keto groups.

Regarding the ionized forms of uracil (or thymine), Sinsheimer *et al.*³²⁷ suggested that uridylic and thymidylic acids ionized at the C-4 and C-2

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- ³⁰⁷ D. Suck and W. Saenger, *J. Amer. Chem. Soc.* **94**, 6520 (1972).
³⁰⁸ H. M. Berman, W. C. Hamilton, and R. J. Rousseau, *Biochemistry* **12**, 1809 (1973).
³⁰⁹ D. Suck, W. Saenger, and J. Hobbs, *Biochim. Biophys. Acta* **259**, 157 (1972).
³¹⁰ D. W. Young and E. M. Morris, *Acta Crystallogr. Sect. B* **29**, 1259 (1973).
³¹¹ C. H. Schwalbe and W. Saenger, *J. Mol. Biol.* **75**, 129 (1973).
³¹² K. N. Trueblood, P. Horn, and V. Luzzati, *Acta Crystallogr.* **14**, 965 (1961).
³¹³ J. Hunt, and E. Subramanian, *Acta Crystallogr. Sect. B* **25**, 2144 (1969).
³¹⁴ D. W. Young, P. Tollin, and H. R. Wilson, *Acta Crystallogr. Sect. B* **25**, 1423 (1969).
³¹⁵ J. Rubin, T. Brennan, and M. Sundaralingam, *Biochemistry* **11**, 3112 (1972).
³¹⁶ J. L. Sussman, N. C. Seeman, S.-H. Kim, and H. M. Berman, *J. Mol. Biol.* **66**, 403 (1972).
³¹⁷ T. D. Sakore and H. M. Sobell, unpublished results (quoted by Sobell²⁹⁴).
³¹⁸ T. D. Sakore, S. S. Tavale, and H. M. Sobell, *J. Mol. Biol.* **43**, 361 (1969).
³¹⁹ T. D. Sakore, H. M. Sobell, F. Mazza, and G. Kartha, *J. Mol. Biol.* **43**, 385 (1969).
³²⁰ A. E. V. Haschemeyer and H. M. Sobell, *Proc. Nat. Acad. Sci. U.S.* **50**, 872 (1963).
³²¹ N. Sundaralingam and J. A. Carrabine, *Biochemistry* **10**, 292 (1971).
³²² M. N. Frey, T. F. Koetzke, M. S. Lehmann, and W. C. Hamilton, *J. Chem. Phys.* **59**, 915 (1973).
³²³ H. M. Sobell and K. Tomita, *Acta Crystallogr.* **17**, 122 (1964).
³²⁴ K. Nakanishi, N. Suzuki, and P. Yamazaki, *Bull. Chem. Soc. Jap.* **34**, 53 (1961).
³²⁵ K. L. Wierzchowski, E. Litońska, and D. Shugar, *J. Amer. Chem. Soc.* **87**, 4621 (1965).
³²⁶ B. I. Sukhorukov, V. T. Aikazyan, and Yu. A. Yershov, *Biofizika* **11**, 753 (1966).
³²⁷ R. L. Sinsheimer, R. L. Nutter, and G. R. Hopkins, *Biochim. Biophys. Acta* **18**, 13 (1955).

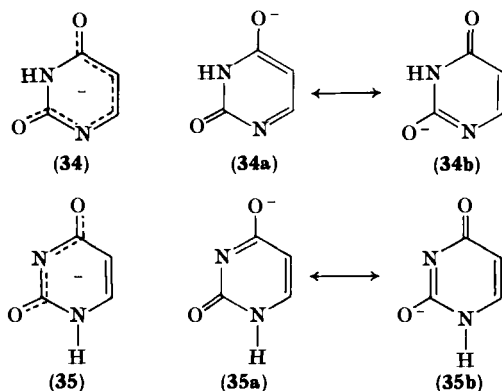
positions to yield forms **33a** and **33b**, respectively. In fact, these two forms are two resonating structures of the same anion (**33**).



Both uracil and thymine deprotonate at N-1 or N-3^{325,326} (forms **34** and **35**, respectively), as initially proposed by Nakanishi *et al.*³²⁴ on the basis of the UV study of anions of uracil and of its N-1- and N-3-methyl derivatives.

Wierzchowski *et al.*³²⁵ recorded in aqueous medium the IR spectra of the monoanions of thymine and of 1-methyl- and 3-methylthymine. The data demonstrated that the monoanions of thymine consist of an equilibrium mixture of two tautomeric forms **34** and **35** corresponding to the dissociation of the N-1 or the N-3 protons, respectively. The fractional content of the thymine monoanion **35** in the mixture of the two monoanions was evaluated from the extinction of the characteristic bands of the anion of thymine and 1-methylthymine to be ~ 0.4 . A marked shift in equilibrium of the tautomers was observed on going from a NaCO in D₂O solution of thymine to NaOD in 75% dioxan-D₂O. Calculation of the tautomeric equilibrium showed that in 75% dioxan the fraction of **35** was 0.25, compared to 0.4 in aqueous medium.

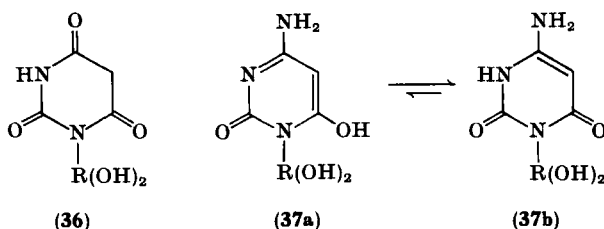
Recent *Raman spectroscopy* studies^{55,56} confirmed the conclusions of IR spectroscopy by showing that uracil and uridine possess the dilactam form and that the possibility that the lactim forms could predominate



in solution should be ruled out. They show also that the removal of a proton (or a deuteron) from uracil substituted at N-1 (1-methyluracil or the uridines) leads to the anionic form of type **33** (or **35**) as suggested by IR spectroscopy.^{47,50}

As in the case of cytosine, several *NMR* and *NQR* studies were performed in search of the predominating tautomeric structures of uracil and thymine and their nucleotides and nucleosides. Investigation of PMR spectra of these compounds in nonaqueous solvents, such as dimethyl sulfoxide, localized the mobile protons in a number of 5- and 6-substituted uracils.^{59,61,328} These and similar studies^{63,85,329,330} indicated that dilactam structure **32** predominates in uracil compounds in aqueous and nonaqueous solutions as well as in the solid state. Proton and N-15 magnetic resonance spectra of several pyrimidines⁸⁵ confirmed the diketo structure usually ascribed to uracil.

The C-13 magnetic resonance spectra of the naturally occurring uracils⁷⁹⁻⁸¹ have been interpreted in terms of the diketo structures of the compounds. Similarly the triketo structure **36** has been found⁸¹ to predominate for 1-(β -D-ribofuranosyl) barbituric acid by a comparison of C-13 spectra of several model nucleosides. Also in the case of 6-hydroxycytidine the equilibrium lies⁸¹ strongly toward the diketo form **37b** in comparison with the lactim-lactam form **37a**. Very recent N-14



quadrupole resonance studies^{91,92} have also shown that for uracil, 5-bromouracil, thymine, and uridine forms of type **32** predominate.

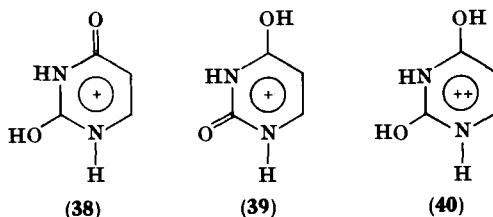
Overall NMR and NQR spectroscopy data thus indicate that the diketo structure predominates for uracil, thymine, and their nucleosides or nucleotides. These studies have failed to detect other tautomeric forms of these compounds.

³²⁸ J. P. Kokko, L. Mandell, and J. H. Goldstein, *J. Amer. Chem. Soc.* **84**, 1042 (1962).

³²⁹ S. Gronowitz, B. Norman, B. Gestblom, B. Mathiasson, and R. A. Hoffman, *Ark. Kemi* **22**, 65 (1964).

³³⁰ R. J. Cushley, I. Wempen, and J. J. Fox, *J. Amer. Chem. Soc.* **90**, 709 (1968).

The protonation of uracil occurs at oxygen to give the protonated monocations **38**, **39** and dication **40**.⁶⁵



From the relative *kinetic* acidities of the O-7 and O-8 protons of 1,3-dimethyluracil dication, Poulter and Anderson³³¹ have concluded that the monocation derived from protonation at O-8 is considerably more stable (as least 3.9 kcal/mole) than its O-7 (**38**) protonated isomer.

Starting from the comparative study of the *ionization constants* of uracil itself as well as of its several methylated or ethylated derivatives (representing models of tautomeric forms), it may be seen (Table XVII) that uracil and uridine exist in aqueous solution in the diketo form **32**. The *pK* values are not known for the model tautomers **27**, **29**, and **30**, but these forms have been ruled out on the basis of UV studies. Recently the ionization constants of uracil, thymine, their derivatives and nucleotides were determined over the range 10–50°, and thermodynamic enthalpy, entropy, and free energy changes for protonation and deprotonation of these compounds have been evaluated.^{93–95,332}

The tautomeric ratios characterizing the whole complex scheme of uracil cannot be evaluated. Only the tautomeric equilibrium constant $K_t^{32,28}$ for uracil was calculated by Katritzky and Waring.⁹⁷ The ionization constants determined by two different methods (see Table XVII) give the values of $\sim 10^{4.0}$ and $\sim 10^{3.3}$ for $K_t^{32,28}$ of 1-methyluracil.

Early work by Austin³³⁶ on the *UV measurements* in ethanol apparently indicated that uracil should be described by the structure **31**, but later Loofbourow *et al.*³³⁷ decided from similar measurements in water that diketo structure **32** dominates (cf. ref. 333). Similarly, Fox

³³¹ C. P. Poulter and R. B. Anderson, *Tetrahedron Lett.*, 3823 (1972).

³³² A. S. Gukovskaya, B. I. Sukhorukov, T. M. Prokopeva, and V. L. Antonovskij, *Izv. Akad. Nauk SSSR, Ser. Khim.* 2682 (1972).

³³³ J. R. Marshall and J. Walker, *J. Chem. Soc.*, 1004 (1951).

³³⁴ P. A. Levene, L. W. Bass, and H. S. Simms, *J. Biol. Chem.* **70**, 229 (1926).

³³⁵ B. I. Sukhorukov, V. I. Poltev, and L. A. Blumenfeld, *Biofizika* **9**, 266 (1964).

³³⁶ J. E. Austin, *J. Amer. Chem. Soc.* **56**, 2141 (1934).

³³⁷ J. R. Loofbourow, M. M. Stimson, and M. J. Hart, *J. Amer. Chem. Soc.* **65**, 148 (1943).

TABLE XVII
COMPARISON OF THE IONIZATION CONSTANTS^a OF URACIL

Type of tautomer	Compound	Ref.:	pK as a base ^{b,c}	pK as an acid ^b			
			97	98, 106	333	334	313
28	1-Methyl-4-methoxyuracil		$+0.65 \pm 0.05$ (1.11 ± 0.08)				
	4-Ethoxyuracil ^d		$+1.00 \pm 0.01$ (1.02 ± 0.02)	10.7	—	—	—
31	2-Ethoxyuracil ^d		—	8.2	8.4 ^{e,f}	—	—
32	Uracil ^{g,h}		-3.38 ± 0.15 (0.53 ± 0.03)	9.5 ^h		9.45 ^f	9.51 ^h
	1-Methyluracil		-3.40 ± 0.12 (0.50 ± 0.05)	9.75		9.71 ^f	9.77
	3-Methyluracil			9.95		9.99 ^f	—
	1,3-Dimethyluracil		-3.25 ± 0.08 (0.57 ± 0.03)	—		—	10.00
	Uridine ^{g,h}			9.25 ^h		—	—

^a Sukhorukov *et al.*³³⁵ have evaluated the ionization constants in the ground and excited states (at $T = 25^\circ\text{C}$) of uridine and uracil.

^b Determined spectrophotometrically unless otherwise indicated.

^c Assuming that bases of different types need not obey the Hammett H_0 function rule.

^d On the basis of UV spectroscopic and ionization constant data, Katritzky and Waring⁹⁷ have suggested form **28** rather than **29** for 4-ethoxyuracil, and IR spectra suggest⁹⁷ the form **31** rather than **30** for 2-ethoxyuracil.

^e The value for 2-methoxy-6-methyluracil.

^f Titrimetric values.

^g For the collection of pK values determined at various ionic strengths and temperatures, see refs. 93 and 96.

^h The pK values for thymine and thymidine have been determined as 9.9 and 9.8, respectively.

and Shugar,^{98,106} who examined the UV absorption spectra of many uracil and thymine derivatives and a number of their nucleosides, have concluded that the compounds existed at neutral pH in aqueous solution in form **32**. All the later papers dealing with the UV spectra of uracils and thymines describe them as corresponding to form **32**, based on comparison with model forms (see refs. e.g., 97, 106, 333, 336). UV studies^{97,106,332} show that uracil and thymine are protonated predominantly on O-8 to give cations of type **39**, while 5-halouracils give cations **38** and **39** in equal proportions.³³²

Both uracil and thymine are deprotonated at N-1 or N-3 to give the anions **34** or **35**, respectively. Studying the UV spectra of alkaline solutions of uracil,^{324,338} halouracils,^{105,325} thymine,^{325,339} and pseudouridine,³⁴⁰ a number of investigators concluded that a mixture of the two anions exists in solution. Some have attempted to evaluate their relative proportion with the help of the spectra of derivatives. The methods involved comparison of the UV spectrum of the singly charged uracil ions with those of the ions of the N-1- and N-3-methyl uracils. The tautomeric constants K_t ^{35,34} as determined by various workers for ions of uracil and its derivatives are listed in Table XVIII. The values are compared with those obtained from the infrared data previously mentioned. It is evident that, on going from aqueous solution to 75–85% dioxan, the proportion of form **35** decreases in the case of thymine and 5-fluorouracil. Halogen substituents cause measurable shifts in the tautomeric equilibrium of the monoanions of uracil. The monoanions of 6-fluoro- and 6-chlorouracil are represented by form **34**, and the contribution of form **35**, if present at all, is very small. The substitution of trifluoromethyl at C-6 causes a tautomeric shift toward form **34** as the UV spectrum of 6-trifluoromethyluracil monoanion³⁴¹ is strikingly similar to that of the monoanion of 3-methyluracil. On the other hand, the monoanions of 5-halouracils are best represented as mixtures of monoanions **35** and **34**, the monoanionic 5-fluorouracil containing a greater proportion of **34**.

Very recently, Shapiro and Kang³³⁸ studied the UV spectrum of uracil in alkali using different buffers. They showed that the spectrum varied considerably with the nature and concentration of the buffer employed. These changes have been ascribed to the influence of the dielectric constant of the medium upon the equilibrium of the uracil monoanions (cf. ref. 325); see footnote *g* to Table XVIII.

³³⁸ R. Shapiro and S. Kang, *Biochim. Biophys. Acta* **232**, 1 (1971).

³³⁹ E. Wittenburg, *Chem. Ber.* **99**, 2391 (1966).

³⁴⁰ R. W. Chambers, *Progr. Nucl. Acid. Res. Mol. Biol.* **5**, 349 (1966).

³⁴¹ A. Giner-Sorolla and A. Bendich, *J. Amer. Chem. Soc.* **80**, 5744 (1958).

TABLE XVIII

CONTENTS OF THE MONOANIONIC FORMS **34** AND **35** IN THE IONS OF URACILS
DETERMINED FROM THE UV SPECTRA^a

References	Compound	(%) Contents of		$K_t^{(35),(34)}$
		35	34	
324	Uracil	51 43	49 57	$\sim 1.0^b$ $\sim 0.8^b$
105	5-F-uracil	r.dom. ^c		
	5-Cl-uracil			$\sim 0.5^d$
	5-I-uracil			$\sim 0.5^d$
	5-Br-uracil	36	64	~ 8.56
	6-F-uracil		dom. ^c	
	6-Cl-uracil		dom. ^c	
326, 335^h	Uracil			~ 10
325	Thymine			1 0.33 ^e
	5-F-uracil	63	37	1.7
339	Thymine	~ 20	~ 80	0.25–0.3 ^f
340	α -Pseudouridine	47	53	~ 0.9
	β -Pseudouridine	17	83	~ 0.2
338^g	Uracil	47	53	~ 0.9

^a Alkaline aqueous solution unless otherwise indicated.

^b Determined from the intensities of the 286 and 258 nm peak, respectively.

^c r.dom. = rather dominant form; dom. = dominant form, probably very small proportion of the other form.

^d Probable contents.

^e In 75% dioxan–water.

^f In 85% dioxan–water.

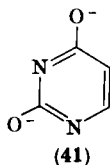
^g Comp. ref. 338 for the effect of the dielectric constant of the medium upon the equilibrium of the monoanions **35** and **34**.

Tautomer **34** predominates in aqueous ammonia solutions, but tautomer **35** is favored by concentrated phosphate buffers of high dielectric constant.

^h In the excited state, the concentration of form **34** becomes much greater than of form **35**, $K_t^{35,34} \approx 0.3 \times 10^{-7}$, see refs. 335, 326.

All UV spectroscopic studies (e.g., refs. 105, 106, 340) show that at pH > 13 uracil and its C-substituted derivatives are best described by the dianionic structure **41** with the negative charges localized on both oxygens.

The *luminescence properties* of uracil and some of its derivatives confirmed the diketo structure of uracil. Longworth *et al.*³⁴² have studied the fluorescence^{342a} and phosphorescence of uracil and some of its derivatives. Both 4-ethoxy-2-pyrimidone and 2,4-dimethoxy-pyrimidine have a strong fluorescence at room temperature, and phos-



phorescence in neutral glasses at 77°K. On the other hand, the N-methyl derivatives of uracil and uracil itself do not fluoresce at room temperature and show only a weak fluorescence at 77°K in neutral glass. The similarity of the luminescence of the latter group of molecules indicate that they exist in the dilactam form **32**.

As the removal of a proton from thymine results in the establishment of a tautomeric equilibrium between its two monoanionic forms,^{342b} the emission spectrum of singly ionized thymine may consist of overlapping spectra of both monoanions. In fact, Gill³⁴⁴ has observed some inconsistencies between the absorption and the fluorescence excitation spectra of thymine in 0.01 *N* NaOH at room temperature. These inconsistencies were of the same kind as those found later by Berens and Wierzchowski,³⁴⁵ who suggested that at room temperature only the thymine monoanion tautomer (**34**) fluoresced, while at 77°K emissions of both monoanionic species contributed to the observed luminescence spectrum.

Recent reports^{351,352} suggested the existence of uracil and thymine as a mixture of tautomeric forms **28** and **32** in aqueous solutions.

³⁴² J. W. Longworth, R. O. Rahn, and R. G. Shulman, *J. Chem. Phys.* **45**, 2930 (1966).

^{342a} Until recently, the naturally occurring pyrimidines had been reported not to fluoresce at room temperature (except for the anion of thymine,³⁴³⁻³⁴⁵ and neutral and anionic forms of 5-methylcytosine³⁴⁶). Very recently a few reports dealt with the room temperature fluorescence of the pyrimidine bases and their nucleotides and nucleosides in neutral aqueous solution.³⁴⁷⁻³⁵²

^{342b} Electron spin resonance measurements on thymine monoanion (triplet state)³⁵³ confirm the deprotonation of thymine from N-1 and/or N-3 atoms.

³⁴³ S. Udenfriend and P. Zaltzman, *Anal. Biochem.* **3**, 49 (1962).

³⁴⁴ J. E. Gill, *J. Mol. Spectrosc.* **27**, 539 (1968).

³⁴⁵ K. Berens and K. L. Wierzchowski, *Photochem. Photobiol.* **9**, 433 (1969).

³⁴⁶ J. E. Gill, *Photochem. Photobiol.* **11**, 259 (1970).

³⁴⁷ P. Vigny, in "The Purines—Theory and Experiment" (E. D. Bergmann and B. Pullman, eds.), p. 311. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1970.

³⁴⁸ P. Vigny, *C.R. Acad. Sci. Ser. D* **272**, 2247 (1971).

³⁴⁹ P. Vigny, *C.R. Acad. Sci. Ser. D* **272**, 3206 (1971).

³⁵⁰ M. Daniels and W. Hauswirth, *Science* **171**, 675 (1971).

³⁵¹ W. Hauswirth and M. Daniels, *Photochem. Photobiol.* **13**, 157 (1971).

³⁵² M. Daniels, *Proc. Nat. Acad. Sci. U.S.* **69**, 2488 (1972).

Daniels³⁵² has shown that the excitation spectra for triplet state formation and fluorescence emission from uracil and thymine in neutral aqueous solution at room temperature were anomalous when compared with the UV absorption spectra of these pyrimidines. These experimental facts have been critically examined with respect to three molecular models, of which the model based on tautomerism of uracil in aqueous solution is, in the opinion of Daniels, the best. The data suggested that the fluorescing tautomer contained an enol group, and the UV data favored the 4-hydroxy structure, i.e., form **28**. The second tautomer, from which the triplet originated, was expected to be the predominant diketo form (**32**).

B. SUBSTITUENT EFFECT ON TAUTOMERIC EQUILIBRIA OF URACIL

It is generally accepted that substitution at C-5 and/or C-6 of the uracil ring does not change significantly the tautomeric equilibrium of uracils. Thus the 5- and 6-halouracils or thymines or the corresponding nucleosides still exist in neutral aqueous solution as well as in the crystalline state in the diketo form **32**. This was shown by X-ray crystallographic studies and by IR, NMR, or UV spectroscopy (e.g., refs. 80, 81, 97, 105, 326, 328, 330, 354–358). The dilactam structure **32** has also been attributed to other derivatives of uracil and thymine, e.g., 6-azauracil nucleosides,³⁵⁹ 5- and 6-trifluoromethyluracils,^{341,360} 6-trichloromethyluracils,³⁶¹ 5-methyluracil nucleosides,³⁶² 5,6-dihydro-uridine.³⁶³

It was shown by several experiments that 5-bromouracil still exists in the dilactam form **32**, but the comparison of ionization constants shows⁹⁷ that $K_t^{32,28}$ for 5-bromo-1-methyluracil is $\sim 10^{3.3}$ or $\sim 10^{1.7}$ depending on the method of estimation. These values can be compared with the corresponding tautomeric constants for 1-methyluracil itself which are $\sim 10^{4.0}$ or $\sim 10^{3.3}$, respectively. Although the two methods give different results, it is clear that the 5-Br substituent causes

³⁵³ R. O. Rahn, *Photochem. Photobiol.* **9**, 527 (1969).

³⁵⁴ Yu. M. Boyarchuk and M. V. Volkenshtein, *Biofizika* **11**, 164 (1966).

³⁵⁵ Y. M. Boyarchuk and M. V. Volkenshtein, *Biofizika* **12**, 777 (1967).

³⁵⁶ A. R. Tarpley and J. H. Goldstein, *J. Amer. Chem. Soc.* **93**, 3573 (1971).

³⁵⁷ K. Berens and D. Shugar, *Acta Biochim. Pol.* **10**, 25 (1963).

³⁵⁸ W. Pfeleiderer and H. Deiss, *Isr. J. Chem.* **6**, 603 (1968).

³⁵⁹ G. T. Rogers and T. L. V. Ulbricht, *Eur. J. Biochem.* **22**, 457 (1971).

³⁶⁰ A. W. Lutz and S. H. Trotto, *J. Heterocycl. Chem.* **9**, 513 (1972).

³⁶¹ A. W. Lutz and S. H. Trotto, *J. Heterocycl. Chem.* **9**, 729 (1972).

³⁶² M. G. Stout and R. K. Robins, *J. Heterocycl. Chem.* **9**, 545 (1972).

³⁶³ M. Sundaralingam, S. T. Rao, and J. Abola, *Science* **172**, 725 (1971).

considerable increase of the proportion of the lactim form (**28**) of 1-methyluracil.

Boyarchuk and Volkenshtein^{354,355} have studied the IR spectra of the crystals of 5-bromo-1-methyl-, 5-bromo-3-methyluracil, and 1-methylthymine and discussed the effect of the electronegative substituents in the pyrimidine ring on the potential energy curve of dimeric hydrogen-bonded complexes of uracil derivatives. Features of the IR spectrum of 5-bromo-1-methyluracil crystal suggested that the stability of the lactim form **28** increases owing to the influence of the substituents.

As far as we are aware, there is no other quantitative evaluation of the influence of substituents on the tautomeric equilibria in uracil except that due to Katritzky and Waring.⁹⁷

C. QUANTUM-MECHANICAL STUDIES

Only in a few cases have attempts been made to interpret the stability of uracil (thymine) tautomers. In Table XIX we list the theoretical quantities relevant to this problem. The methods limited to π -electrons, as already stated, can be used only to predict the *tendencies* to undergo tautomerization in a series of related molecules, so the results of this type of work are not presented here. The calculated changes in enthalpy (ΔH) upon tautomeric conversion show that in the ground state the tautomeric equilibrium is greatly shifted toward lactam form **32**. Comparing the ΔH value of 4.29 kcal/mole for guanine¹⁴⁸ with that for uracil and thymine (see Table XIX), we see that guanine is more inclined to show the lactim form than uracil or thymine. In the first excited singlet and in the ionic states the situation is, however, opposite to that in the ground state: here both uracil and thymine are more inclined than guanine¹⁴⁸ ($\Delta H \sim 14.6$ – 19.2 kcal/mole) to pass to the rare tautomeric form. The CNDO/2 CI calculations by Bertrán *et al.*¹⁵⁰ on the change of tautomeric constant K_t ^{32,38} upon excitation predict a shift toward the normal dilactam form **32** in the first singlet excited state, but no change for the first triplet state.

The CNDO/2 calculations correctly predict tautomers **32** of uracil and thymine to be more stable than tautomers **28**. It is interesting to observe that 5-fluorouracil is predicted to be more easily converted into lactim form **28** than uracil and thymine, considering that 5-fluorouracil is mutagenic. As to the relative stability of uracil tautomers, the different approaches give different results. For instance, the π -SCF MO calculations¹⁴⁹ including σ -polarization effect¹⁵¹ predict the relative stability of uracil tautomers to be **32** > **31** > **29** > **28** > **27**, while the CNDO/2 approach¹⁵⁶ gives the order **32** > **27** > **31** > **29** > **30** > **28**.

TABLE XIX
THEORETICAL QUANTITIES^a CHARACTERIZING THE TAUTOMERIC STABILITY OF URACILS AND THYMINES

Method	References	Compound	Quantity ^b (kcal/mole)
π -HMO + σ -Del Re	Berthod and Pullman ¹⁴⁵⁻¹⁴⁷	Thymine	$\Delta E = -24.2$
π -SCF MO + σ -Del Re	Danilov ^{148,6}	Uracil	$\Delta H_{S_0} = 7.62, \Delta H_{S_1} = -12.05$ $\Delta H_{(+)} = -9.82, \Delta H_{(-)} = +0.74$
		Thymine	$\Delta H_{S_0} = 7.99, \Delta H_{S_1} = -9.22$ $\Delta H_{(+)} = -1.55, \Delta H_{(-)} = 3.38$
π -SCF MO ^c	Bodor <i>et al.</i> ¹⁴⁹	Uracil	$\Delta H_a^{32,31} = -17.96$ $\Delta H_a^{32,29} = -23.93$ $\Delta H_a^{32,28} = -29.91$ $\Delta H_a^{32,27} = -33.59$
CNDO/2 ^d	Fujita <i>et al.</i> ¹⁵²	Uracil	$\Delta E = -10.43$
		5-F-uracil	$\Delta E = -9.96$
		Thymine	$\Delta E = -11.92$
CNDO/2 CI	Bertrán <i>et al.</i> ¹⁵⁰	Uracil	$\Delta E_{S_1} - \Delta E_{S_0} = 19.46$ $\Delta E_{T_1} - \Delta E_{S_0} = 0$
		Thymine	$\Delta E_{S_1} - \Delta E_{S_0} = 18.54$ $\Delta E_{T_1} - \Delta E_{S_0} = 0.23$

^a For theoretical quantities characterizing the relative tendency of uracils to undergo tautomerization see refs. 138-141, 144-147.

^b See Table VI for explanation of abbreviations. All quantities characterize the conversion **32** \rightleftharpoons **28**, except those indicated.

^c The method includes σ -polarization.

^d Using the same geometrical positions for heavy atoms of the two tautomers. For other CNDO/2 study of tautomeric stability of uracil, see refs. 153, 156.

These differences as well as the different magnitudes of the energy differences between the most stable tautomer, **32** and the rare form **28** are not unexpected, as the geometrical structures of minor tautomers are not known.

The results presented in Table XIX are thus not very unsatisfactory. It would be interesting to calculate the changes in tautomeric equilibrium of uracil on 5- or 6-halo-substitution, particularly the 5-bromo-compound.

It should be added that Snyder *et al.*³⁶⁴ have predicted by means of nonempirical calculations that thymine anion **34** should be more stable than **35** in the gas phase by 21 kcal/mole. It is difficult, however, to compare this figure with tautomeric ratios of the thymine anionic forms in aqueous or in dioxan-water solution.

V. Electronic Structure of the Ground State of Uracils and Thymines

The aim of this section is to discuss the physicochemical properties of uracil and thymines and to give a theoretical interpretation of these properties. Since the experimental evidence indicates that uracil and thymine exist essentially in lactam form **32**, our discussion will be principally restricted to this form.

A. THE GEOMETRY OF URACIL AND THYMINES

Information on the geometrical structure of uracil is available as in the case of cytosine from X-ray crystallographic studies. The geometry of thymine is known also from recent neutron diffraction experiments. The structures of both uracil and thymine have been reviewed by several authors.^{7,160,162,167} Recently Voet and Rich⁷ analyzed the reliable crystal structures of uracils and uridines and their complexes and of several compounds containing the thymine ring, and presented averaged values of bond lengths and bond angles for uracil and thymine. During the last three to four years, the number of uracil and thymine structures determined has increased greatly. The differences between the averaged bond lengths and bond angles as listed in ref. 7; the corresponding averaged structural parameters, obtained more recently by ourselves by including the new crystallographic results,^{267,277-279,289-291,301-309,313-316,318,319,321} are small.

³⁶⁴ L. C. Snyder, R. G. Shulman, and D. B. Neumann, *J. Chem. Phys.* **53**, 256 (1970).

Several MO methods have been applied to calculate the π -electronic bond orders (or total bond overlap populations) of uracil, thymine, and some of their derivatives. They can be found in the following papers: π -HMO calculations on uracils and thymines, see reviews^{1,140,170-172}; π -SC HMO (ω -technique) calculations¹⁶⁹ on forms **32** and **28** of uracil and thymine, 1-methyluracil and 1-methylthymine; π -SCF MO calculations on uracil forms **32**,^{140,144,173,174,178-180,365} **28**,^{144,178} **27**, **29-31**,¹⁷⁸ on forms **32** and **28** of 5,6-dihydrouracil,¹⁸¹ thymine, forms **32**,^{171,173,174,179,280,366} **28**,¹⁴⁰ adenine-thymine base pair^{171,184-186} [for the π -bond order of the C(5)-C(6) bond in uracil, thymine, 6-azathymine, 5-amino-, 5-nitro- and 6-methyluracil, and orotic acid see refs. 6, 187, 189, 296]; π -SCF MO + σ -Del Re calculations¹⁹⁰ on forms **28** of uracil and thymine, the pair of 2-NH₂-purine (amine form) with thymine (form **32**); EHT calculations on uracil,^{191,367} uridine,¹⁹¹ thymine,³⁶⁷ dihydro-uracil and dihydrothymine,³⁶⁷ *cis-syn* thymine dimer,³⁶⁷ substituted dihydrouracils and dihydrothymines,³⁶⁸ 6-azauridine³¹¹; CNDO/2 calculations on uracil and 5,6-dihydrouracil³⁶⁹; *nonempirical* calculations (overlap charge densities) on thymine and its anionic forms.³⁶⁴

The values of the π -bond orders have been used to predict bond lengths in uracil^{1,149} and thymine.¹⁶⁹ The qualitative agreement between predicted and experimental values is in general good, as in the case of cytosine. Recently, Geller *et al.*³⁶⁹ have calculated the CNDO/2 total overlap populations for uracil and 5,6-dihydrouracil and compared the differences of bond lengths in these molecules with the corresponding negative differences of overlap population. The correlation obtained between theoretical and experimental data is quite good.

The Mulliken bond overlap populations calculated³¹¹ by EHT method for 6-azauridine have been compared with those for uridine,¹⁹¹ and the differences between them were used to interpret the changes in the geometry of uridine caused by the 6-aza substitution.

In all the quantum-mechanical calculations the assumption is generally made that the uracil and thymine rings are planar. Observed deviations are within the limits of experimental accuracy. The exocyclic oxygens appear to deviate most from planarity.

³⁶⁵ J. Ladik and K. Appel, Report QB20, Quantum Chemistry Group, Uppsala Univ., Uppsala.

³⁶⁶ A. Denis and A. Pullman, *Theor. Chim. Acta* **7**, 110 (1967).

³⁶⁷ F. Jordan and B. Pullman, *Theor. Chim. Acta* **10**, 423 (1968).

³⁶⁸ F. Jordan, *Theor. Chim. Acta* **11**, 390 (1968).

³⁶⁹ M. Geller, A. Kaliński, W. Kołos, and M. Kopczyńska, *Biochim. Biophys. Acta* **287**, 1 (1972).

B. VIBRATIONAL SPECTRA

As mentioned previously (Section III) IR and Raman spectroscopic studies have been carried out to elucidate the structure of the main tautomers of uracil and thymine. Although the vibrational spectra of the pyrimidine bases (e.g., refs 41, 50, 51, 55, 326, 354, 370) are difficult to interpret, a better understanding of the vibrational motions of these molecules has been possible over the past years.^{193,370-372} There have also been some quantum-mechanical attempts to interpret the vibrational spectra.

Snyder *et al.*³⁶⁴ have computed the overlap charge densities (which correspond to the bond orders) by means of the *ab initio* calculations for thymine and its anions and concluded that the computed changes of bond orders in thymine monoanions relative to thymine itself were in agreement with the direction and relative magnitude observed for changes in the IR spectra.³²⁵ More recently, a quantitative theoretical reconstitution of the IR spectra of the hydrogen bonds in molecular crystals of both 1-methylthymine and uracil has been given.^{373,374} The crystal IR spectra of the hydrogen bond show a distinct fine structure which is strongly influenced by deuteration. The theoretical spectra^{373,374} are in good agreement both in frequency and intensity with experiment.^{370,372,374} The theoretical model³⁷⁵ predicts that after deuteration the so-called "distortion parameter," describing the difference in the potential energy for the low-frequency vibration between the ground and excited states of the high-frequency vibration, should be divided by the factor $\sqrt{2}$. The substantially different structures of the IR absorption bands of the deuterated 1-methylthymine and uracil were in agreement with this theoretical prediction.

Considerable attention has also been devoted by several investigators to the theoretical study of the potential curves for hydrogen bonds of the guanine-cytosine and adenine-thymine base pairs. An accurate representation of this potential is important because the genetic code is contained in this interaction. Löwdin has suggested that mutations may be a result of a shift in position of the hydrogen bond protons in the base units of DNA via proton tunneling.^{5,376-379} The idea of proton

³⁷⁰ Y. Kyogoku, S. Higuchi, and M. Tsuboi, *Spectrochim. Acta, Part A* **23**, 969 (1967).

³⁷¹ I. Harada and R. C. Lord, *Spectrochim. Acta, Part A* **26**, 2305 (1970).

³⁷² H. Susi and J. S. Ard, *Spectrochim. Acta, Part A* **27**, 1549 (1971).

³⁷³ A. Witkowski and M. Wójcik, *Chem. Phys. Lett.* **20**, 615 (1973).

³⁷⁴ A. Witkowski and M. Wójcik, *Chem. Phys. Lett.* **26**, 327 (1974).

³⁷⁵ Y. Marechal and A. Witkowski, *J. Chem. Phys.* **48**, 3697 (1968).

³⁷⁶ P. O. Löwdin, *Rev. Mod. Phys.* **35**, 724 (1963).

transfer between bases has been suggested also by Kyogoku *et al.*³⁸⁰ on the basis of the IR study of DNA. Although the arguments of these authors have been questioned,³⁸¹ other IR studies^{335,382} seem to be in line with the concept of a proton transfer. On the other hand, recent IR studies³⁸³ of base-pairing models of DNA (1:1 mixed crystals of 9-methyladenine and 1-methylthymine and of 9-ethylguanine and 1-methylcytosine) have not shown any proton transfer processes at temperatures between -150 and $+30^{\circ}\text{C}$.

Some information³⁸⁴⁻³⁸⁶ on the absorption spectra (X-H stretching) of base pairs became available, and it was interesting to test the results of calculations on the hydrogen-bond potential energy surfaces for the base pairs by comparing them with experimentally known quantities.

All original calculations indicated that the potential wells in the DNA base pairs were indeed double. The first calculations of the guanine-cytosine potential have been performed by Ladik³⁸⁷ by means of a rather crude electrostatic model, and these have been followed by more sophisticated quantum mechanical calculations including the σ electrons of the hydrogen bonds.^{183,388-391} The motion of the protons in the hydrogen bonds of the guanine-cytosine and/or adenine-thymine base pairs have been studied later by a number of investigators.^{171,185,217,392,393} *Ab initio* calculations on the guanine-cytosine H-bond potential by Clementi *et al.*²⁶⁴ have shown that this potential was not double, but contained rather a slight hump. Using the potential cross sections from the papers of Harris and Rein³⁹⁰ and of Lunell and Sperber,³⁹² Parker and Every³⁹⁴ have calculated the vibrational energy levels and tunnel-

³⁷⁷ P. O. Löwdin, *Biopolym. Symp.* **1**, 161 (1964).

³⁷⁸ P. O. Löwdin, *Biopolym. Symp.* **1**, 293 (1964).

³⁷⁹ P. O. Löwdin, in "Electronic Aspects of Biochemistry" (B. Pullman, ed.) p. 167. Academic Press, New York, 1964.

³⁸⁰ Y. Kyogoku, M. Tsuboi, T. Shimanouchi, and J. Watanabe, *Nature (London)* **189**, 120 (1961).

³⁸¹ B. I. Sukhorukov and G. I. Matkhanov, *Biofizika* **8**, 131 (1963).

³⁸² H. T. Miles, *Nature (London)* **183**, 1814 (1959).

³⁸³ H. Fritzsche, *Experientia* **27**, 507 (1971).

³⁸⁴ J. Piřha, R. N. Jones, and J. Piřhova, *Can. J. Chem.* **44**, 1044 (1966).

³⁸⁵ Y. Kyogoku, R. C. Lord, and A. Rich, *J. Amer. Chem. Soc.* **89**, 496 (1967).

³⁸⁶ B. R. Parker and G. P. Khare, *J. Mol. Spectrosc.* **41**, 195 (1972).

³⁸⁷ J. Ladik, Preprint QB8, Quantum Chemistry Group, Uppsala University, 1963.

³⁸⁸ R. Rein and F. E. Harris, *Science* **146**, 649 (1964).

³⁸⁹ R. Rein and F. E. Harris, *J. Chem. Phys.* **42**, 2177 (1965).

³⁹⁰ R. Rein and F. E. Harris, *J. Chem. Phys.* **43**, 4415 (1965).

³⁹¹ R. Rein and F. E. Harris, *J. Chem. Phys.* **45**, 1797 (1966).

³⁹² S. Lunell and G. Sperber, *J. Chem. Phys.* **46**, 2119 (1967).

³⁹³ D. K. Rai and J. Ladik, *J. Mol. Spectrosc.* **27**, 79 (1968).

³⁹⁴ B. R. Parker and J. Van Every, *Chem. Phys. Lett.* **8**, 94 (1971).

ing times at each level for the normal base pairs adenine-thymine and guanine-cytosine and for the forms guanine-thymine, guanine-excited cytosine, and guanine-cytosine anion. The lifetimes of the proton on the various levels have also been calculated. These authors have also discussed the distribution and tunneling of the protons on the levels for various densities of radiation and shown that considerable tunneling could take place for radiation in resonance with the levels.

Two papers have attempted to compare the observed infrared lines of the base pairs in the region of the hydrogen-bond absorption with the calculated data. Rein and Svetina³⁹⁵ have calculated the proton vibrational states and relative transition probabilities for two guanine-cytosine hydrogen bonds. Their preliminary results seemed to be consistent with the absorption peak at 3489 cm^{-1} (0.436 eV) reported by Piřha *et al.*³⁸⁴ for the hydrogen bond N-H stretching mode of guanine-cytosine complex (calc.³⁹⁵: $\sim 0.5\text{ eV}$). More recently, Parker and Khare³⁸⁶ have measured the IR spectra of single and double DNA and performed the calculations of the energy levels for several curves of the hydrogen bond in guanine-cytosine and adenine-thymine base pairs. The expected proton frequencies have been compared with experimental IR spectra. This type of comparison is useful to gain insight into the accuracy of theoretical hydrogen bond potential curves for the pairs. Unfortunately, the observed IR lines did not correlate exactly with the predicted values. This is not unexpected since the problem is a complicated one, and there are several reasons for discrepancy between theory and experiment (difficulties in identification of an absorption, one dimensional model of calculation, neglected vibrational coupling, etc.).

C. DISTRIBUTION OF ELECTRON DENSITIES

Since uracil and thymine, like cytosine, are fundamental nucleic acid bases, they have been treated by many methods of quantum chemistry in view to establish the essential electronic characteristics of their ground states.

1. *Distribution of π -Electron, σ -Electron and Total Electron Density*

The π -charge and σ -charge densities as well as total electron densities in uracils and thymines have been calculated abundantly. The charge distributions or gross atomic populations for uracils and thymines calculated by different methods can be found in the following papers:

³⁹⁵ R. Rein and S. Svetina, *Int. J. Quant. Chem.* **1s**, 171 (1967).

for π -HMO calculations, see reviews^{1,140,170-172} (cf. also ref. 396); π -SC HMO (ω -technique) calculations¹⁶⁹ on forms **32** and **28** of uracil, thymine, 1-methyluracil and 1-methylthymine; π -SCF MO calculations on uracil, forms **32**,^{140,144,148,149,171,173,174,176-178,180,199-203,205,206,365,397} **28**,^{144,177,178} **29**,^{144,178} **27**, **30**, **31**,¹⁷⁸ 1- and 3-methyl- and 1,3-dimethyluracil,²⁰⁸ forms **28** and **32** of 5,6-dihydrouracil,^{144,181} 5-fluorouracil,³⁹⁷ uracil substituted at positions 5 or 6 by F, Cl, Br, I, OH, OCH₃, SH, NH₂, CH₃, or COOH,²⁰⁵ cationic and anionic forms of uracil,^{177,202,207} thymine, forms **32**,^{171,173-175,180,201-203,205,206,366} **28**,¹⁴⁰ 1-methylthymine,²⁰¹ thymine substituted at positions 5 or 6 by F, Cl, Br, I, OH,

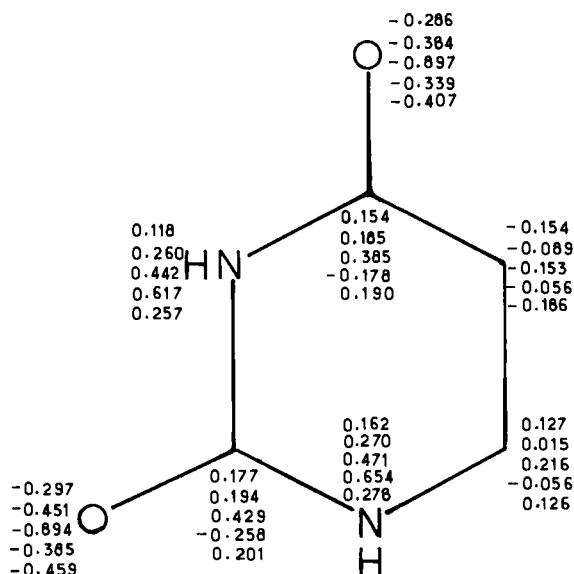


FIG. 10. Net π -charges in uracil calculated by different methods (from top to bottom: π -HMO, π -SCF MO, EHT, IEHT, CNDO/2). Data taken from Pullman and Pullman.^{1,222,223,228}

OCH₃, SH, NH₂, CH₃, or COOH,²⁰⁵ adenine-thymine base pair^{171,175,184,185} and its cationic and anionic forms²⁰⁹ (for the charge densities at C-5 and C-6 positions in uracil, thymine, 5-amino- 5-nitro- and 6-methyluracil, 6-azathymine and orotic acid, see refs. 187, 188); π -HMO + σ -Del Re calculations on uracil,^{369,397} 5-fluoro- and 5-bromouracil,³⁹⁷ 5,6-dihydrouracil and its anionic form³⁶⁹; π -SCF MO + σ -Del Re

³⁹⁶ R. Zahradník, J. Koutecký, J. Jonáš, and J. Gut, *Collect. Czech. Chem. Commun.* **28**, 1499 (1963).

³⁹⁷ H. Berthod, C. Giessner-Prettre, and A. Pullman, *Theor. Chim. Acta* **8**, 212 (1967).

calculations on forms **28** or uracil and thymine,¹⁹⁰ forms **32** and **28** of 1-methylthymine,²¹⁰ form **32** of 5-bromo-1-methyluracil²¹⁰ and on the pair¹⁹⁰ of 2-aminopurine (amine form) with thymine (form **32**); *EHT* calculations on uracil and uridine,¹⁹¹ 5-halouracils,³⁵⁶ thymine,^{356,367} dihydrouracil, dihydrothymine, and *cis-syn* thymine dimer³⁶⁷ and on several substituted dihydrouracils and dihydrothymines,³⁶⁸ uridine,¹⁹¹ 6-azauridine³¹¹; *IEHT* calculations on uracil^{211,212} and thymine²¹²;

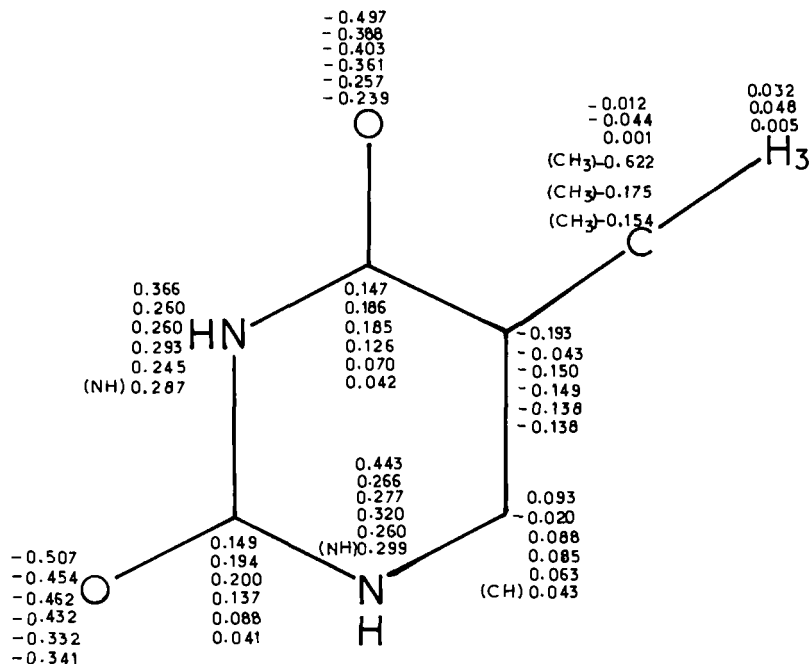


FIG. 11. Net π -charges in thymine calculated by different methods (from top to bottom: π -HMO,¹⁴⁰ π SCF MO,³⁶⁶ CNDO/2,²¹⁴ and nonempirical^{219,220,364}). For the nonempirical charge distributions in anionic forms of thymine, see ref.364. The symbols NH, CH, or CH₃ indicate that the charge for the whole group of atoms is given.

CNDO/2 calculations on uracil,^{214,229,369} 5,6-dihydrouracil,³⁶⁹ and thymine^{214,215} [cf. the paper by Labhart and Herrmann²¹⁶ on *SCF MO* calculations including π - and σ -electrons (electrostatic approximation) on thymine], also see Figs. 10–13]; *INDO* calculations on uracil²²⁹; *nonempirical* calculations on uracil,²²⁹ thymine,^{219,220,364} and anions of thymine.³⁶⁴

In Figs. 10–13 we have presented π -charges and total densities in uracil and thymine as calculated by different methods. The calculations

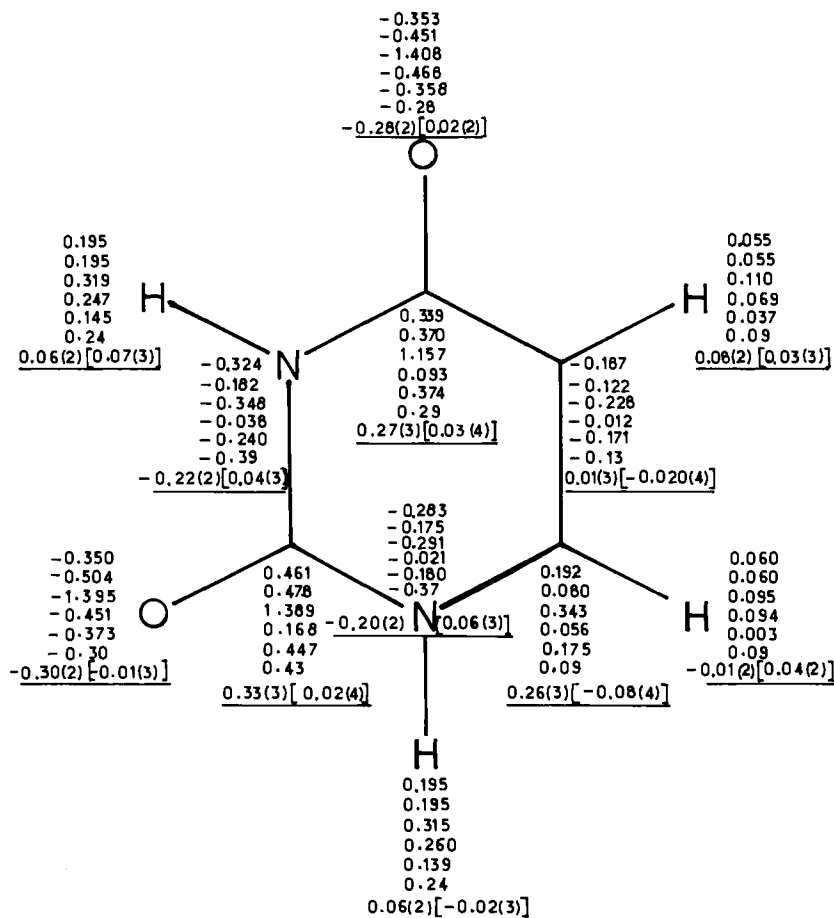


FIG. 12. Total net charges in uracil calculated by different methods (from top to bottom: π -HMO + σ -Del Re, π -SCF MO + σ -Del Re, EHT, IEHT, CNDO/2, nonempirical). Data taken from Pullman and Pullman^{1,222,223,228} and from Stewart²²⁹ (nonempirical). Experimental²²⁹ net gross valence atomic populations for uracil are underlined [two sets of experimental numbers were obtained by the use of the L-shell standard STO's and L-shell SCF AO's scattering factors (in brackets), respectively]. The estimated standard deviations referring to the last decimal place are given in parentheses.

predict a negative π -charge and total charge on C-5. Negative charges are concentrated also on O-7 and O-8. Methyl substitution at C-6 does not change the order of the π -charges, i.e., still $q_7 > q_8 > q_5$. Negative π -charge may be found on carbon atom of the methyl group of thymine. The negative π -charges on the oxygens are of considerable magnitude in

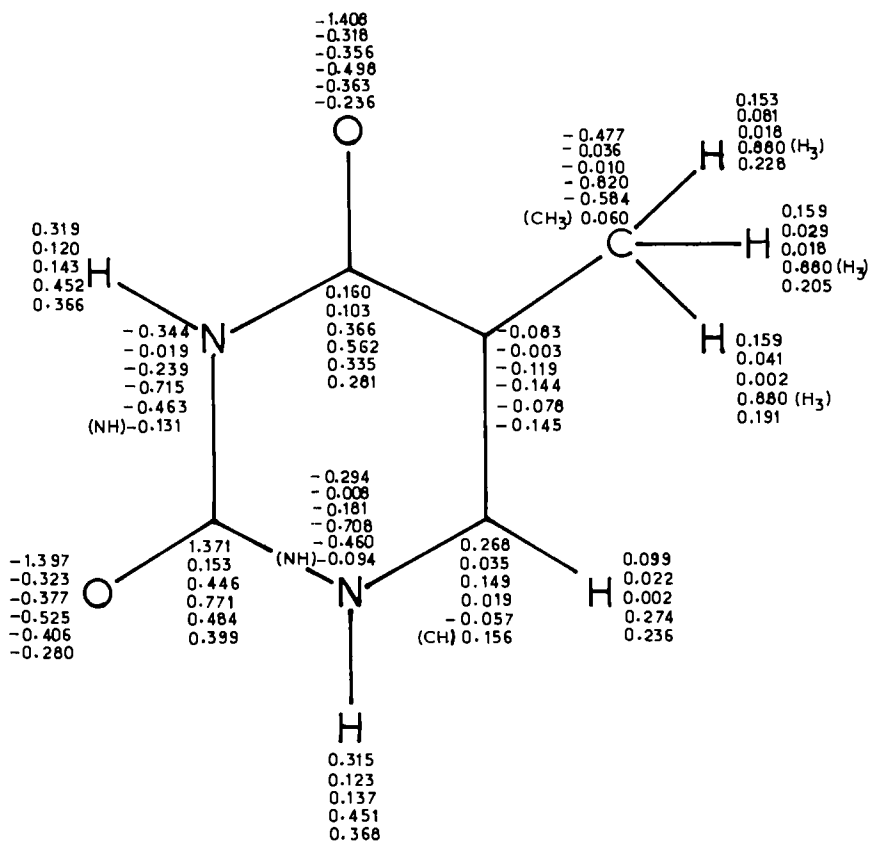


FIG. 13. Total net charge in thymine calculated by different methods (from top to bottom: EHT,³⁶⁷ IEHT,²¹² CNDO/2,²¹⁴ and nonempirical^{219,220,364}). For the nonempirical charge distributions in anionic forms of thymine, see ref. 364. The symbols NH, CH, CH₃ or H₃ indicate that the charge for the whole group of atoms is given.

comparison to that on C-6 (similarly as in cytosine). All (including nonempirical) calculations give the following order of total negative charge densities in both uracil and thymine: N-3 > N-1 > C-5 and O-7 > O-8 (or O-8 ≥ O-7) > C-5. Semiempirical methods predict again that the negative charges on oxygens are greater than those on nitrogens, while nonempirical calculations^{219,220} (except the calculation³⁶⁴ with a minimum set of atomic-orbital basis functions) give the opposite order of the charge distributions. Similarly to the π -electron charges, the total densities on C-2, C-4, and C-6 are, in general, positive.

In the case of uracil it is possible to make a comparison between the

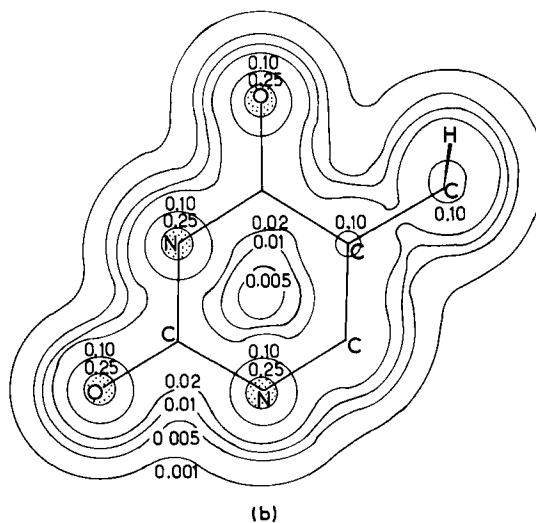
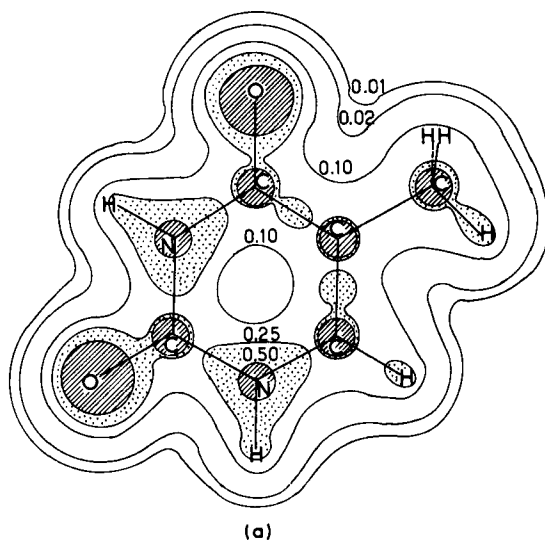


FIG. 14. Contours of constant values of electron density in the molecular plane of thymine (a) and in a plane parallel to the molecular plane at 0.8 atomic unit from it (b).²³⁰ Values as indicated.

theoretical charge distributions and experimental ones determined by Stewart²²⁹ from an analysis of the generalized X-ray scattering factors applied to the crystal. The agreement of the STO L-shell X-ray valence charges with the theoretical calculations is fairly good (Fig. 12). The most important exceptions is for atom C-5, for which the experimental charge is 3.99 ± 0.03 electrons, while the theoretical values are rather greater than 4.1 electrons.

Pullman *et al.*²³⁰ have suggested that the isodensity contours maps from the nonempirical wave functions could be helpful for a better understanding of the real electron distribution in a molecule. On the other hand, valence-electron density maps have been Fourier synthesized³⁹⁸ from X-ray diffraction data of uracil, and although the last technique is not expected to give quantitative electron density maps, such maps may serve as a qualitative probe for further studies of valence structure. It is also interesting to compare the theoretical isodensity map for thymine²³⁰ with the experimental valence density map for uracil.³⁹⁸ The two maps (Fig. 14 and 15) are very similar to each other. They show the directed valence structure about the nitrogen atoms and along the C-O bonds. Both the theoretical and experimental maps give the typical triangular form of densities on N-H groups and nearly spherical distributions on oxygens. In both

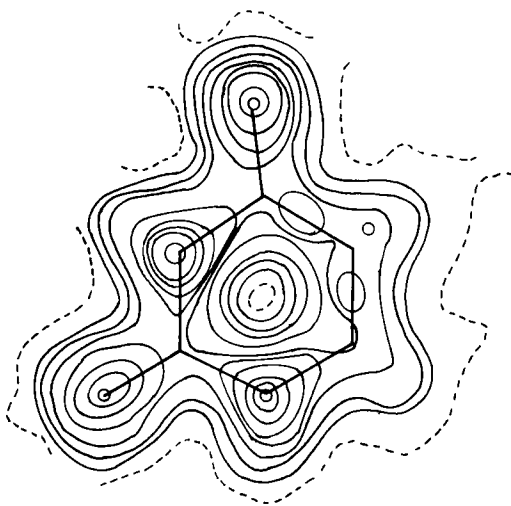


FIG. 15. Valence Fourier difference map for uracil in the least-squares plane of the C, N, and O atoms. Rearranged from ref. 398.

³⁹⁸ R. F. Stewart, *J. Chem. Phys.* **48**, 4882 (1968).

cases the density along the double bond C(5)–C(6) is greater than that along the C(4)–C(5) bond.

2. Dipole Moments

Known dipole moments of uracil, thymine, and their derivatives including nucleosides are collected in Tables XX and XXI. Most of these have been measured during the last two years. On the other hand, the dipole moments of uracil and thymine, and of some derivatives, were calculated by quantum mechanical methods a long time ago (see Table XXII). All the methods, except the EHT and IEHT ones, give reasonable values of the dipole moments of the bases with the moment of thymine being smaller than that of uracil. The substitution of a methyl group at N-1 or N-3 does not change considerably the dipole moment of the parent molecule. The CNDO/2 calculations³⁶⁹ have predicted that the dipole moment of uracil upon hydrogenation at C-5 and C-6 should decrease by about 0.8 D. This value seems to be reasonable as hydrogenation of 1,3,5-trimethyluracil decreases its dipole moment by about 0.30 (Table XX).⁴⁰⁴

As to the direction of the dipole moments in the ground state of the molecules, two kinds of experimental measurements are available. Stewart²²⁹ has calculated the X-ray dipole moment of uracil within the point-charge approximation using the atomic charges for a standard STO L-shell. The calculated dipole moment is 4.0 ± 1.3 D and its direction of $71^\circ \pm 12^\circ$ from N-1–C-4 toward N-3 atom. These values obtained within a point-charge model have an estimated standard error of about 30%. Nevertheless, the X-ray dipole moment is of reasonable magnitude and in close agreement with the value of 4.1 D obtained by solution measurement of uracil in dioxan³⁹⁹ (Table XX).

The second experimental measure of the orientation of the dipole moment in the ground state of the bases was made by Seibold and Labhart⁴⁰⁵ for uracil and thymine. The direction of the ground state dipole moment with respect to the transition moment in the lowest excited singlet state has been determined from the influence of an

³⁹⁹ I. Kułakowska, M. Geller, B. Lesyng, and K. L. Wierzchowski, *Biochim. Biophys. Acta* **361**, 119 (1974).

⁴⁰⁰ P. Mauret and J. P. Fayet, *C.R. Acad. Sci., Ser. C* **264**, 2081 (1967).

⁴⁰¹ H. Weiler-Feilchenfeld and E. D. Bergmann, *Isr. J. Chem.* **6**, 823 (1968).

⁴⁰² I. Kułakowska and K. L. Wierzchowski, *Studia Biophys.* **34**, 109 (1972).

⁴⁰³ R. F. W. Hopmann, *Ber. Bunsenges. Phys. Chem.* **77**, 52 (1973).

⁴⁰⁴ B. Weinblum, F. P. Ottensmeyer, and G. F. Wright, *Biochim. Biophys. Acta* **155**, 24 (1968).

⁴⁰⁵ K. Seibold and H. Labhart, *Biopolymers* **10**, 2063 (1971).

TABLE XX: DIPOLE MOMENTS OF URACILS AND THYMINES

Compound	Dipole moment (D)	Solvent ^a	References
Uracil ^{b,c}	4.16 ± 0.04	d	399
1-Methyl	4.15 ± 0.01	—	399
3-Methyl	4.18 ± 0.01	—	399
5-Methyl (thymine)	3.95 ± 0.04	—	400
	4.13 ± 0.03	—	399
5-Ethyl	4.01 ± 0.03	—	399
5-Bromo	4.64	d	401
	4.5 ± 0.3	—	233
	4.15 ± 0.01	d	399
5-Iodo	4.01 ± 0.02	—	399
5-Nitro	5.47 ± 0.02	—	399
6-Methyl	4.64 ± 0.02	—	399
1,3-Dimethyl	3.9 ± 0.1	d	233
	5.18 ± 0.05	d	400
	3.98 ± 0.01	b	402
	4.16 ± 0.01	d	399
1,5-Dimethyl	4.10 ± 0.02	—	399
5-Ethyl-1-methyl	4.02 ± 0.02	—	399
1,6-Dimethyl	4.65 ± 0.02	—	399
1-Isobutyl-6-methyl	4.27 ± 0.7 ^d	b	403
3,5-Dimethyl	4.07 ± 0.02	d	399
3,6-Dimethyl	4.55 ± 0.03	—	399
5,6-Dimethyl	4.66	d	401
	4.55 ± 0.01	d	399
6-Ethyl-5-methyl	4.65 ± 0.02	—	399
5-Ethyl-6-methyl	4.50 ± 0.02	—	399
1,3,5-Trimethyl	3.93 ± 0.02	b	402
	4.08 ± 0.01	d	399
5-Ethyl-1,3-dimethyl	3.89 ± 0.02	b	402
	4.03 ± 0.01	d	399
5-Chloro-1,3-dimethyl	3.91 ± 0.02	b	402
5-Bromo-1,3-dimethyl	3.90 ± 0.02	—	399
	4.11 ± 0.01	d	399
5-Iodo-1,3-dimethyl	3.78 ± 0.03	b	402
	4.00 ± 0.02	d	399
1,3-Dimethyl-5-nitro	5.19 ± 0.01	b	402
	5.43 ± 0.01	d	399
1,3,6-Trimethyl	4.45 ± 0.01	b	402
	4.64 ± 0.02	d	399
6-Chloro-1,3-dimethyl	3.06 ± 0.01	—	399
5,6-Dihydro-1,3,5-trimethyl ^e	3.61 ± 3.65	b (23°)	404

^a d = dioxan, b = benzene. Temperature = 25°C unless otherwise stated.

^b The experimental X-ray dipole moment of uracil is 4.0 ± 1.3 D (71°).²²⁹

^c The orientation of the dipole moment in the ground state of uracil (26 ± 3° or 45 ± 3° depending on the assumed direction of transition moment) and thymine (29 ± 2°) has been determined⁴⁰⁶ from the influence of an electric field on the light absorption of the molecules in solution.

^d Determined from a chemical relaxation study by means of the dipolar chemical field effect.

^e Dipole moment of three isomeric tetramethylthymine dimers have been also measured.

TABLE XXI
DIPOLE MOMENTS OF URACIL AND THYMINE NUCLEOSIDES^a

Nucleoside		Dipole moment (D)	References
Base	Sugar		
Uracil	Ribose	5.08 ± 0.05	400
		5.01 ± 0.02	406
	2'-Deoxyribose	5.25 ± 0.01	406
	2',3'-Isopropylideneribose	4.5 (d)	237
	2',3'-Isopropylidene-5'-tritylribose	4.4 (d)	237
5-Methyluracil	Ribose	4.2 (b)	237
		4.86 ± 0.02	406
	2'-Deoxyribose	4.71 ± 0.05	400
		5.25 ± 0.01	406
6-Methyluracil	Ribose	4.48 ± 0.03	406

^a Dipole moments were measured in dioxan at 25°C except those indicated (d, dioxan; b, benzene).

electric field on the light absorption of the molecules in solution. The estimated directions depend, however, on the assumed direction of the transition moment of the excited state of the molecule. Adopting the orientation of the transition moment as given for 1-methylthymine in ref. 408 or as given for 1-methyluracil in ref. 409, the direction of the ground state dipole moment of uracil has been determined to be $26 \pm 3^\circ$ or $45 \pm 3^\circ$, respectively. The last value is in a better agreement with the theoretically predicted one (cf. Table XXII). The orientation of the dipole moment was set at $29 \pm 2^\circ$ for thymine.

It is interesting to look at the effect of substituents on the dipole moment of uracil (or thymine). An examination of the data collected in Table XX shows that among the four positions (N-1, N-3, C-5, C-6) available for substitution, the one at C-6 is the most sensitive. An alkyl substituent at C-6 of uracil (or thymine) increases the dipole moment by about 0.4–0.5 D, while the same substituent at N-1, N-3, or C-5 has only a small effect. Similarly, a halogen does not greatly alter the dipole moment of the molecule when at C-5 whereas 6-halogen decreases the value of the dipole moment considerably (cf. the data for 1,3-dimethyluracil and for its 5- and 6-chloro derivatives, Table XX). An attempt has been made by Kułakowska and Wierzchowski⁴⁰² to interpret these

⁴⁰⁶ I. Kułakowska, A. Rabczenko, and D. Shugar, *Biochem. Biophys. Res. Commun.* **48**, 65 (1972).

⁴⁰⁷ K. Nishimoto, *Bull. Chem. Soc. Jap.* **40**, 2493 (1967).

⁴⁰⁸ R. F. Stewart and L. H. Jensen, *J. Chem. Phys.* **40**, 2071 (1964).

⁴⁰⁹ W. Eaton and T. P. Lewis, *J. Chem. Phys.* **53**, 2164 (1970).

results by vector addition of bond moments with the experimental dipole moment of 1,3-dimethyluracil. In general, a good agreement between experimental and calculated moments has been obtained. The π -HMO (with Pullman's parameters) and σ -Del Re methods have been applied^{409a} to calculate the dipole moments of several uracils. The results are in reasonable agreement with experimental values.

The PCILO method has been applied^{237,238} to calculate the dipole moments of several conformers of uridine and deoxyuridine (see footnote *a* to Table XXII). However, at present, it is difficult to make a detailed comparison of the calculated dipole moments of nucleosides with the experimental data. In solution, the nucleosides exist as a mixture of several conformers in unknown proportions.

3. Molecular Isopotential Maps—Chemical Reactivity

Electrostatic molecular potential-energy maps in the plane of the ring of thymine as well as in a plane parallel to the ring plane of the molecule have been calculated²⁴⁴ using nonempirical wave functions (Fig. 16). Thymine has two carbonyl oxygens. Potential-energy curves indicate two regions of attraction for a proton toward these oxygens, the rest of the molecule being repulsive. The directionality of the attraction is influenced by the environment, as in the case of cytosine. The oxygen, which is surrounded by an NH group on both sides, presents one symmetrical potential well. On the other hand, two minima appear near the oxygen which has one NH neighbor and one CMe group on the other side. The depth of the minima in thymine is much smaller than that of the corresponding wells in cytosine. This is in excellent agreement with the observation that thymine and thymidine are much less basic than cytosine²⁴⁹ (or cytidine) and explains also the fact that thymine does not undergo alkylation in conditions under which the other bases react.^{248,249,410,411} The positions and depths of the potential wells are thus undoubtedly connected with the ease of the electrophilic attack.

As concerns the hydration sites of thymine, the interaction energy (its electrostatic component) between thymine and water has been

^{409a} The calculations have been performed by M. Geller from Warsaw University.

The dipole moments (in D) for uracils are as follows (the experimental data from Table XX are given in parentheses): uracil 3.9 (4.16), 1-Me-uracil 4.0 (4.15), 3-Me-uracil 3.7 (4.18), 5-Me-uracil (thymine) 3.7 (4.1), 6-Me-uracil 4.6 (4.6), 5-Br-uracil 4.1 (4.15), 5-I-uracil 4.1 (4.0), 1,5-di-Me-uracil 3.5 (4.1), 3,5-di-Me-uracil 3.8 (4.1), 1,6-di-Me-uracil 4.6 (4.65), 3,6-di-Me-uracil 4.6 (4.6), 5,6-di-Me-uracil 4.4 (4.66).

⁴¹⁰ B. C. Pal, *Biochemistry* 1, 558 (1962).

⁴¹¹ J. J. Christensen, J. H. Rytting, and R. M. Izatt, *Biochemistry* 9, 4907 (1970).

TABLE XXII
DIPOLE MOMENTS OF URACILS AND THYMINES^a CALCULATED BY DIFFERENT THEORETICAL METHODS

Method	References	Molecule ^b	Dipole moment ^d		
			$\mu_\pi(\alpha_\pi)^e$	$\mu_\sigma(\alpha_\sigma)^f$	$\mu_{\text{tot}}(\alpha_{\text{tot}})^g$
π -HMO ^c	233	1,3-DiMe-uracil	3.86 (37)	0.2 (270)	3.7 (35)
		1-Me-thymine	3.86 (37)	0.4 (254)	3.5 (33)
π -SC HMO	169 ^h	Uracil	2.51 (9)	—	3.45 (11)
		Thymine	2.31 (17)	—	3.26 (16)
π -HMO + σ -Del Re	145, 146, 234 ^h	Uracil			3.6 (39)
		1,3-DiMe-uracil	3.5 (28)	0.6 (82)	3.8 (35)
	224	Thymine	2.9	0.91	3.56
		1-Me-thymine	2.8 (29)	0.94 (73)	3.54 (39)
	397	Uracil	3.2	0.9	3.9
		5-F-uracil	3.0	1.3	3.7
		5-Br-uracil	3.20	1.45	3.98
π -SCF MO + σ -Del Re	235, 397	Uracil	3.3	0.9	4.0 (35)
		5-F-uracil	3.1	1.3	3.7
	366	Thymine			4.0
	208	1,3-DiMe-uracil	3.5 (32)	0.9 (73)	4.2 (40)
EHT ⁱ	191, 228	Uracil			(*)12.3 (41)

IEHT	211	Uracil	4.76 (19.4)	2.16 (75.3)	(*)7.63 (36)
	212	Uracil			4.28
		Thymine			4.53 ^f
CNDO/2 ^k	214	Uracil	4.20 (29)	1.21 (190)	(*)4.61 (36)
		Thymine	3.94 (33)	1.20 (187)	(*)4.35 (39)
<i>Ab initio</i>	219, 226	Thymine	—	—	4.22 (50)
	220	Thymine	—	—	3.3
	364	Thymine	—	—	3.45 (42)

^a The evaluation of the dipole moment of uridine as a function of the rotation about the glycosidic bond has been carried out by the PCILO method by Weiler-Feilchenfeld *et al.*²³⁷ (for the C_{2'}-endo *gg* and C_{3'}-endo *gg* conformations). The same method has been used by Berthod and Pullman²³⁸ to calculate the dipole moments of *anti* and *syn* conformers of uridine, C_{2'}-endo *gg* (7.0 and 3.4 D, respectively) and those of deoxyuridine, C_{2'}-endo *gg* (4.8 and 4.8 D, respectively). For the π -contributions for the dipole moments of uracils see refs. 174, 177, 407.

^b All the data refer to form **32** of a molecule.

^c Cf. reviews,^{1,222-228}

^d Dipole moment in Debye units; the angles (in degrees) with the axis N(1)—C(4) (measured counterclockwise) are given in parentheses.

^e π -Component of the dipole moment.

^f σ -Component of the dipole moment (hybridization moment not included).

^g Total dipole moment (hybridization moment included * or nor included).

^h Dipole moment of the adenine-thymine base pair has also been calculated.

ⁱ For dipole moments of derivatives of dihydrouracils and dihydrothymines, see ref. 368, and for dipole moments of dimers of thymine and dihydrothymine, see ref. 367.

^j Included dipole moment of lone pairs.

^k For other CNDO/2 calculations on dipole moment of uracils see refs. 150, 153, 215, 369.

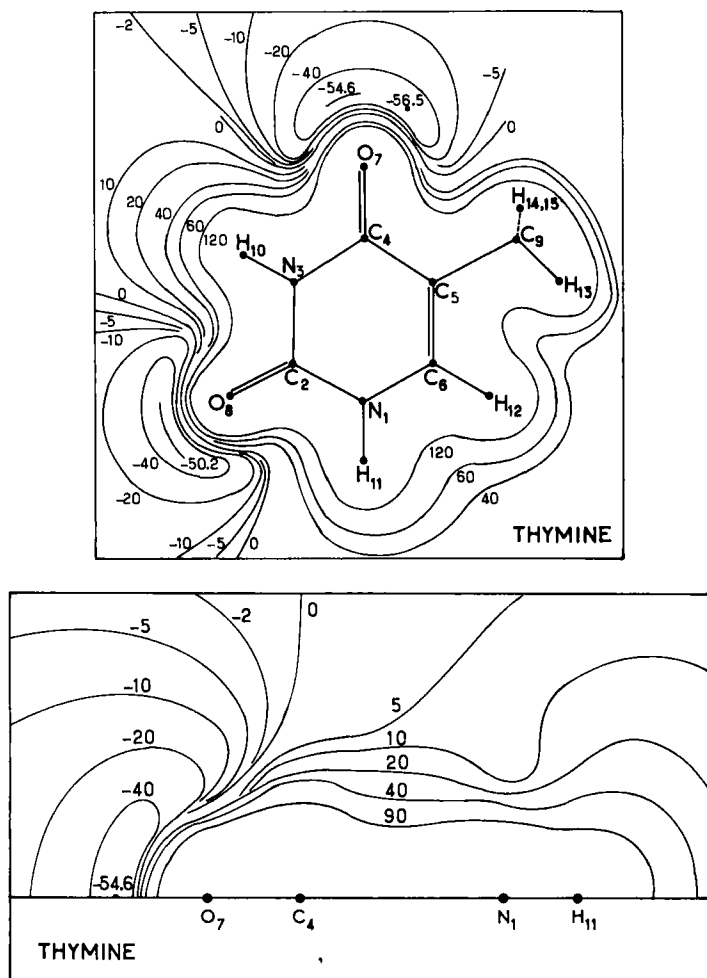


Fig. 16. Electrostatic molecular potential-energy maps for thymine²⁴⁴ in the ring plane (top) and in the plane perpendicular to the ring plane and passing through atoms as indicated (bottom).

calculated²⁵² using nonempirical wave functions of the molecules.²²⁰ There are two symmetrically placed hydration sites in thymine on each side of the O-7 oxygen (Fig. 17). Both take advantage of the attraction of the neighboring NH group for the oxygen of water, and the planar arrangement is only very slightly favored over the perpendicular one. Another favorable site for hydration exists between N-3-H and O-8 oxygen, both coplanar and perpendicular conformations being very similar in bonding energies.

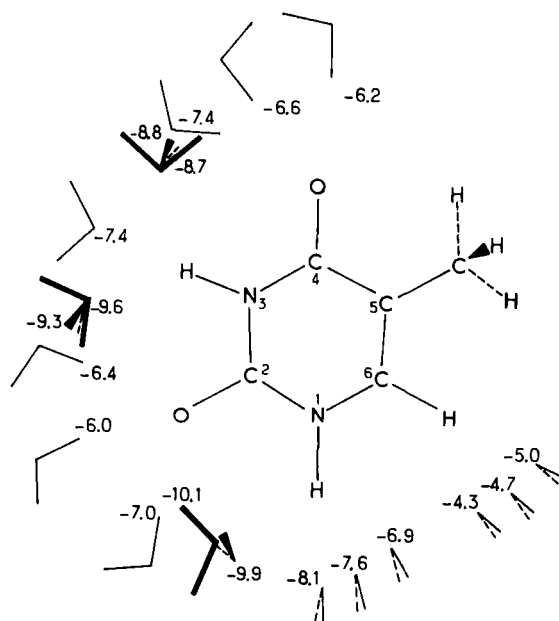


FIG. 17. Hydration sites in thymine.²⁵² Energies in kilocalories per mole. Heavy lines, preferred hydration sites; full lines, coplanar arrangement of water and base; half-dashed lines, perpendicular arrangement of water with respect to the plane of the base.

D. MOLECULAR ORBITAL ENERGIES: ELECTRON-DONATING AND ELECTRON-ACCEPTING PROPERTIES

In Table XXIII we have collected the ionization potentials of uracil, its derivatives, and thymine. There is an overall agreement between theoretical values of the ionization potentials and the corresponding experimental data (see Table XXIV). The relative electron-donor properties of the pyrimidine bases are given experimentally by the following order of the increasing value of ionization potentials: cytosine < thymine < uracil, and the calculated results predict, in general correctly, this order. The evaluation of the lone-pair ionization potentials of uracil (thymine) and cytosine by the π -SCF MO method²⁵⁷ and the CNDO/2 method shows that uracil (thymine) is a worse n(O)-donor than cytosine. As with cytosine, all tautomers of uracil (Tables XXV and XXVI) have the lowest ionization potential as well as the lowest electron affinity of the π -type. Conversion of uracil into the 5,6-dihydro derivative changes the energies of the molecular orbitals of the molecule; the π -HMO calculations³⁶⁹ on uracil and its 5,6-dihydro derivative

TABLE XXIII
IONIZATION POTENTIALS (eV) OF URACILS AND THYMINES

Compound	Ref.:	254 ^a	253 ^b	255 ^c
Uracil		9.82 ± 0.1	9.47	8.48
5-Br-uracil		—	—	8.25
6-Me-uracil		—	—	7.90
6-Azauracil		10.18 ± 0.1	—	—
Thymine		9.43 ± 0.1	8.94	8.25

^a Mass spectrometry.

^b Photoionization by mass spectrometry.

^c From the spectra of charge-transfer complexes.

TABLE XXIV
THE CALCULATED π -SCF MO IONIZATION POTENTIALS AND ELECTRON
AFFINITIES OF URACILS AND THYMINES^a

Reference	Molecule	I^b (eV)	A^b (eV)
257 ^c	Uracil	9.0 10.0 ^d n(O-8) 10.3 ^d n(O-7)	
235 ^c	Uracil	9.15	-0.38
397 ^c	5-F-uracil	8.9	
366 ^c	Thymine	8.8	-0.41
208 ^c	1-Me-uracil	8.83	-0.34
	3-Me-uracil	9.07	-0.34
	1,3-diMe-uracil	8.83	-0.34
258	Uracil	9.16 ^e	0.02 ^e
149	Uracil	11.27 (10.90) ^f 9.24 (8.82) ^f	1.33 -0.86

^a Compare the following papers for the discussion of the energies of occupied and unoccupied molecular orbitals of uracil and thymine, and of their complexes with different partners: uracil,^{171,173,177,178,182,200,201,203,207,259,260,407,412} thymine,^{171,184,186,201,260} adenine-thymine,^{184,186,190,208} 2-NH₂-purine-thymine,¹⁹⁰ uracil-uracil, uracil-uracil-uracil, thymine-thymine, and thymine-thymine-thymine.¹⁷¹

^b Ionization potential (I) and electron affinity (A) calculated from Koopmans' theorem except those indicated.

^c Using the corrected π -SCF MO procedure (an empirical diminution of the values of atomic valence-state ionization potentials).

^d The lone-pair ionization potentials calculated according to Nakajima and Pullman.²⁶¹

^e Corrected values (the molecular orbital energies were decreased by a constant value).

^f Calculated by the "half-electron" method of Dewar *et al.*²⁶² The I values correspond to the adiabatic ionization potential.

TABLE XXV
ENERGIES OF THE LOWEST EMPTY (LEMO) AND THREE HIGHEST OCCUPIED (HOMO) MOLECULAR ORBITALS
IN URACIL AND THYMINE^a CALCULATED BY ALL-VALENCE AND ALL-ELECTRON METHODS

Method: Ref.:	EHT	IEHT		CNDO/2	<i>Ab initio</i>		
	224	212	211	214	220	218, 219	364
Uracil							
LEMO (eV)	—	-7.69 π	—	—	—	—	—
HOMO (eV)	-12.71 π	-9.01 σ^b	-9.43 σ	-11.88 π	—	—	—
	-13.37 σ	-9.19 σ^c	-9.89 σ	-12.90 σ	—	—	—
	-13.90 π	-9.83 π	-11.08 π	-13.18 π	—	—	—
Thymine							
LEMO (eV)	—	-7.56 π	—	—	—	2.29 π	2.9 π
HOMO (eV)	—	-8.95 σ^c	—	-11.37 π	-10.54	-10.16 π	-8.6 π
	—	-9.05 σ^b	—	-12.85 σ	-12.15	-11.91 π	-9.6 π
	—	-9.43 π	—	-13.10 π	-12.70	-12.11 σ^c	-10.1 σ

^a Snyder *et al.*³⁶⁴ have also calculated the molecular orbital energies of anionic forms of thymine by *ab initio* method.

^b Mainly localized on O-7.

^c Mainly localized on O-8.

TABLE XXVI

ENERGIES^a OF THE LOWEST EMPTY (LEMO) AND THREE HIGHEST OCCUPIED (HOMO) MOLECULAR ORBITALS IN URACIL CALCULATED BY CNDO/2 METHOD¹⁵⁶

Tautomer	LEMO (eV)	HOMO (eV)		
32	2.25	-11.81	-12.86	-13.05 σ
27	3.22	-12.85	-13.04 σ	-14.22
28	1.94	-11.12	-11.77 σ	-13.59 σ
29	1.97	-10.86	-12.39 σ	-14.18 σ
30	2.42	-10.33	-11.62 σ	-13.34 σ
31	2.12	-10.72	-12.32 σ	-13.57 σ

^a Unlabeled orbitals are π levels.

show that the preferred tautomer of the latter is a poorer electron acceptor and donor than tautomer **32** of uracil.

The energies of the molecular orbitals of the adenine-thymine base pair have been calculated by several authors to elucidate the effect of hydrogen bond formation on the properties of the bases (for π -HMO calculations, see refs. 1, 140, 171, 263).

The π -SCF MO calculations on the pair and on the isolated molecules show that the molecular orbitals of the adenine-thymine pair are slightly perturbed with respect to adenine or thymine (compare the

TABLE XXVII

ENERGIES OF HIGHEST OCCUPIED (HOMO) AND LOWEST EMPTY (LEMO) MOLECULAR ORBITALS OF ADENINE, THYMINE, AND THEIR PAIR CALCULATED BY π -SCF MO METHOD (CLOSED-SHELL)^a

Reference	MO	Adenine	Adenine-thymine ^b	Thymine
184, 209	LEMO (eV)	-1.19	-1.05	
	HOMO (eV)	-9.65	-1.97 (2.05)	-1.94 (2.04)
			-9.45 (9.38)	
186			-10.24	-10.23 (10.13)
	LEMO (eV)	0.004	0.16	
			-1.25	-1.32
	HOMO (eV)	-10.27	-10.09	
			-11.63	-11.69

^a Except those indicated.

^b The values of the ionization potentials and electron affinities calculated by the open-shell method are given in parentheses.

results of the calculations on guanine-cytosine base pair, Section III). The two highest occupied molecular orbitals of the adenine-thymine pair as well as its two lowest empty molecular orbitals originate from the corresponding molecular orbitals of adenine and thymine, as in the case of the guanine-cytosine base pair. Thus the electron-donor and electron-acceptor properties of the adenine-thymine pair depend mainly on these properties of adenine and thymine, respectively (Table XXVII). As to the comparison of these properties in the two base pairs, the π -SCF MO method predicts that the electron-donor and electron-acceptor capacity of the adenine-thymine pair should be smaller than those of the guanine-cytosine pair.

VI. Electronic Excited States of Cytosine, Uracil, Thymine, and Their Derivatives

The study of the optical properties of naturally occurring pyrimidines and purines is a problem of great interest in molecular biology. The knowledge of these properties provide information important for understanding energy transfer, hypochromism, photochemistry, optical rotatory dispersion, circular dichroism, magnetic optical rotatory dispersion, and magnetic circular dichroism of DNA, RNA, and related model systems. Here, we discuss those aspects of the electronic excited states of the pyrimidine bases which have been investigated by quantum-mechanical methods.

A. ELECTRONIC ABSORPTION SPECTRA

Many studies on the spectroscopic properties in the near and far ultraviolet region of cytosine, uracil, thymine, their derivatives, nucleotides and nucleosides have been made in recent years. DeVoe and Tinoco,⁴¹³ for instance, following previous efforts by other investigators,^{414,415} have extended to short wavelengths (~ 185 nm) the measurements of the absorption spectra of the four deoxyribonucleosides of DNA. Marshall and Walker³³³ have analyzed the UV spectra of 2,4-disubstituted pyrimidines, and Shugar and Fox^{98,106} examined the spectra of the pyrimidine bases of the nucleic acids and their

⁴¹² M. Tanaka and S. Nagakura, *Theor. Chim. Acta* **6**, 320 (1966).

⁴¹³ H. DeVoe and I. Tinoco, *J. Mol. Biol.* **4**, 518 (1962).

⁴¹⁴ G. H. Beaven, E. R. Holiday, and E. A. Johnson, in "The Nucleic Acids" (E. Chargaff and J. N. Davidson, eds.), p. 493. Academic Press, New York, 1955.

⁴¹⁵ E. Fredericq, A. Oth, and F. Fontaine, *J. Mol. Biol.* **3**, 11 (1961).

nucleosides as a function of pH. The UV absorption spectra down to 185 nm for a number of synthetic polynucleotides in the helical and random forms, as well as those for their constituent mononucleotides and corresponding nucleosides and for the free bases have been presented by Voet *et al.*,⁴¹⁶ and Clark and Tinoco⁴¹⁷ have attempted to systematize and characterize the spectral bands of the pyrimidine and purine bases. These last investigators have developed an assignment scheme which, in their opinion, correlates the bands in the various compounds. They classify the observed transitions into three groups named B_{2u} , B_{1u} and E_{1u} by analogy with the corresponding bands in benzene. However, in the light of recent studies on circular dichroism of nucleoside derivatives, our understanding of the properties of the electronic excited states of these compounds seems far from complete. Miles *et al.*⁴¹⁸⁻⁴²¹ have prepared derivatives of cytosine and uracil and studied their circular dichroism and absorption properties to clarify the relation between their spectroscopic and conformational properties. The results for cytosine nucleosides⁴¹⁹ gave clear evidence for four electronic transitions in these bases above 190 nm related to the B_{2u} , B_{1u} , and E_{1u} bands of benzene. Several cytosine nucleosides appeared to possess only two well-resolved absorption maxima around 270 nm and 198 nm (cf. ref. 416), but manifest also additional absorption between these limits. Such additional absorption occurs usually as a peak at ~ 235 nm.^{104,413,422} Miles *et al.*⁴¹⁹ have also found another band perturbing the long-wavelength side of the very intense 198 nm absorption peak at about 215 nm. Thus there are four electronic transitions (of the $\pi \rightarrow \pi^*$ type), according to Miles *et al.*⁴¹⁹ in the CD spectra of cytidine derivatives down to 190 nm. The data suggest that the assignments of Clark and Tinoco⁴¹⁷ may not be correct. While the observed absorption bands of cytosine at 276, 237, 204, and 184 nm have been related by Clark and Tinoco to the B_{2u} , B_{1u} , and E_{1u} (doubly degenerate) bands of benzene, Miles *et al.*⁴¹⁹ attributed this assignment to first four $\pi \rightarrow \pi^*$ transitions of cytidine near 270, 240, 220, and 195 nm, and suggest that the absorption at 184 nm may be a fifth $\pi \rightarrow \pi^*$ band in the molecule.

⁴¹⁶ D. Voet, W. B. Gratzer, R. A. Cox, and P. Doty, *Biopolymers* **1**, 193 (1963).

⁴¹⁷ L. B. Clark and I. Tinoco, *J. Amer. Chem. Soc.* **87**, 11 (1965).

⁴¹⁸ D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.* **91**, 824 (1969).

⁴¹⁹ D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.* **91**, 831 (1969).

⁴²⁰ D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *Int. J. Quant. Chem.* **3s**, 129 (1969).

⁴²¹ D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *J. Amer. Chem. Soc.* **92**, 3872 (1970).

⁴²² L. B. Clark, G. G. Peschel, and I. Tinoco, *J. Phys. Chem.* **69**, 3615 (1965).

There is controversy regarding the band at ~ 230 – 240 nm of cytosine. Originally, Miles *et al.*⁴²³ considered this band as due to an $n \rightarrow \pi^*$ transition because of the large blue shift upon protonation (cf. also ref. 424). Later, on the basis of the circular dichroism studies of 2'-deoxycytidine, they revised their assignment^{419,420} and agreed that its origin is probably $\pi \rightarrow \pi^*$. A fluorescence polarization study on 5-methylcytosine⁴²⁵ seems also to indicate that the 235 nm band covers a $\pi \rightarrow \pi^*$ transition because the 270 nm ($\pi \rightarrow \pi^*$) and 235 nm bands have transition moments nearly parallel to each other. Lewis and Eaton⁴²⁶ could not find any $n \rightarrow \pi^*$ transition down to 230 nm in cytosine monohydrate by the study of its polarized single-crystal absorption spectrum, and optical rotary studies on azacytidines³⁵⁹ did not show any $n \rightarrow \pi^*$ transitions down to the 200 nm region. On the other hand, Rich and Kasha⁴²⁷ found an $n \rightarrow \pi^*$ transition around 280 nm in the more complicated polycytidylic acid, from polarized absorption measurements on oriented film. Altogether, there is no experimental evidence for $n \rightarrow \pi^*$ bands in cytosine itself or its nucleoside or nucleotide in the region between the longest wavelength band and the absorption at ~ 200 nm.

In uracil and thymine, and their nucleosides and nucleotides, two distinct regions of absorption are usually observed, one located near 260–270 nm and the second near 200 nm. An additional band at ~ 180 nm has been found in uracil and 1,3-dimethyluracil in the vapor phase and in aqueous or trimethyl phosphate solution.^{417,422} Clark and Tinoco⁴¹⁷ assigned the absorption at ~ 260 nm in uracil to the B_{2u} band and those at ~ 200 and ~ 180 nm to the E_{1u} degenerate bands. They did not find any weak absorption in the region between 260 and 200 nm of uracil which could be attributed to the B_{1u} type, but this type of absorption appeared at 229 nm in 6-azauracil in trimethyl phosphate. In CD spectra of uridine derivatives Miles *et al.*⁴¹⁸ (cf. also ref. 424) have observed two peaks (usually of opposite sign) in the spectral region spanned by the 260 nm absorption, which suggested that it contains two overlapping absorption bands. Similarly two CD peaks are found in the region of the 200 nm absorption system. Altogether there are thus four absorption bands in the CD spectra of uridine derivatives in the region of 260–270 to ~ 200 nm. These bands have been considered by

⁴²³ D. W. Miles, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U.S.* **57**, 1138 (1967).

⁴²⁴ W. Voelter, R. Records, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.* **90**, 6163 (1968).

⁴²⁵ P. R. Callis, W. T. Simpson, *J. Amer. Chem. Soc.* **92**, 3593 (1970).

⁴²⁶ T. P. Lewis and W. A. Eaton, *J. Amer. Chem. Soc.* **93**, 2054 (1971).

⁴²⁷ A. Rich and M. Kasha, *J. Amer. Chem. Soc.* **82**, 6197 (1960).

Miles *et al.*⁴¹⁸ to be of the $\pi \rightarrow \pi^*$ type and correlated with the B_{2u} , B_{1u} , and E_{1u} bands of benzene. The absorption at ~ 180 nm in uracil, according to Miles *et al.*,^{418,421} covers a fifth $\pi \rightarrow \pi^*$ transition. A recent study⁴⁰⁵ of the influence of an electric field on the light absorption of uracil and thymine in solution confirms that in the region < 255 nm the long-wavelength band of uracil overlaps a second transition which is hidden in the absorption spectrum. Similarly, in thymine the second transition appears below 275 nm. In both cases, however, no conclusion as to the nature of the weak bands was given.

A few attempts have been made to observe the $n \rightarrow \pi^*$ transitions in uracils. No Cotton effect derived from an $n \rightarrow \pi^*$ transition is observed in the CD spectrum of uridine. Such transitions are observed in some 6-azauracil nucleosides,³⁵⁹ but they are located at the long-wavelength side of the first $\pi \rightarrow \pi^*$ band (B_{2u}). On the other hand, Eaton and Lewis⁴⁰⁹ on the basis of the polarized single-crystal absorption spectrum of 1-methyluracil have found $n \rightarrow \pi^*$ transition at 264 nm, i.e., at the high-energy side of the longest wavelength $\pi \rightarrow \pi^*$ absorption band at 275.5 nm. It is possible, however, that crystal interactions change the relative positions of the two absorption bands (strong $\pi \rightarrow \pi^*$ and weak $n \rightarrow \pi^*$) which are close together in energy.

Spectral data (λ_{\max} and ΔE , and $\epsilon \times 10^{-3}$) for the pyrimidine bases investigated in a few representative papers are collected in Table XXVIII. The absorption bands are denoted by the capital letters A, B, C, etc. In Table XXVIII we have listed the results of the vacuum ultraviolet measurements by Yamada and Fukutome⁴²⁸ (cf. also ref. 429), who measured the spectra of sublimed films of cytosine, thymine, uracil (and also of guanine and adenine) down to 120 nm at room temperature. Several remarkable absorption peaks were found below 190 nm in addition to the already known ones near 260 and 200 nm. A weak absorption at 230–240 nm in cytosine was not indicated in the sublimed films of the molecule,⁴²⁸ but was visible in the stretched polyvinyl alcohol film spectrum.⁴³² Crewe *et al.*⁴³⁰ studied the interactions of fast electrons with the five nucleic acid bases and measured the energy-loss spectra of ~ 20 keV electrons transmitted through thin films of these bases. These last data are also listed in Table XXVIII for comparison with the other spectral findings.

Theoretical calculations on the electronic absorption spectra of the

⁴²⁸ T. Yamada and H. Fukutome, *Biopolymers* **6**, 43 (1965).

⁴²⁹ J. W. Preiss and R. Setlow, *J. Chem. Phys.* **25**, 138 (1956).

⁴³⁰ A. V. Crewe, M. Isaacson, and D. Johnson, *Nature (London)* **231**, 262 (1971).

⁴³¹ H. F. Stewart and N. Davidson, *J. Chem. Phys.* **39**, 255 (1963).

⁴³² A. F. Fucaloro and L. S. Forster, *J. Amer. Chem. Soc.* **93**, 6443 (1971).

TABLE XXVIII
NEAR- AND FAR-UV SPECTRAL DATA^a FOR CYTOSINE, URACIL, AND THYMINE

Reference (solvent)	A (B _{2u})	B (B _{1u})	C'	D'	E	F	G
<i>1. Cytosine</i>							
DeVoe and Tinoco ⁴¹³ (H ₂ O, neutral pH) ^b	271, 4.57 (0.18)	230, 5.39 (0.19)	—	197, 6.29 (0.60)	—	—	—
Voet <i>et al.</i> ⁴¹⁶ (H ₂ O, pH = 8.8)	267, 4.64 (6.1)	—	—	196.5, 6.31 (22.5)	—	—	—
(H ₂ O, pH = 8.2) ^c	271, 4.57 (9.1)	s230, 5.39 (8.2)	—	198, 6.26 (23.2)	—	—	—
Clark <i>et al.</i> ⁴²² (vapor)	s290, 4.28						
Clark and Tinoco ⁴¹⁷ (H ₂ O, pH = 7)	267, 4.64	230, 5.39	s290 ^d , 5.93	—	—	—	—
(TMP) ^e	277, 4.48 (7.5)	s237, 5.23 (3.5)	—	204, 6.08 (11.09)	185, 6.70 ^k (12.2)	—	—
Morita and Nagakura ¹⁰⁴ (H ₂ O, neutral pH)	266, 4.65 (0.110)	236, 5.25	—	197, 6.29 (0.678) ^f	—	—	—
Miles <i>et al.</i> ⁴¹⁹ (H ₂ O, pH = 7) ^g	270, 4.59	~ 240, 5.17	~ 220, 5.64	195, 6.36	—	—	—
	271, 4.57	~ 242, 5.15	~ 218, 5.68	195, 6.36	—	—	—
Yamada and Fukutome ⁴²⁸ (sublimed films) ^h	271–270 4.57–4.59	—	—	203–199 6.11–6.23	—	161, 7.70	150, 8.27
Crewe <i>et al.</i> ⁴³⁰ (energy losses) ⁱ	~ 264, 4.7 ± 0.2	—	—	~ 191, 6.5 ± 0.1	—	—	~ 149, 8.3 ± 0.2
<i>2. Uracil and Thymine</i>							
DeVoe and Tinoco ⁴¹³ (H ₂ O, neutral pH)	Thymine ^l 267, 4.64 (0.22)	—	—	206, 6.02 (0.33)	—	—	—

(continued)

TABLE XXVIII (*Continued*)

Reference (solvent)	A (B _{2u})	B (B _{1u})	C'	D'	E	F	G
Voet <i>et al.</i> ⁴¹⁶	Uracil						
(H ₂ O, pH = 7)	259.5, 4.77 (8.2)	—	—	202.5, 5.13 (9.2)	—	—	—
(H ₂ O, pH = 7.3) ^m	261, 4.75 ^m (10.1)	—	—	205, 6.05 ^m (9.8)	—	—	—
	Thymine						
(H ₂ O, pH = 7.0)	264, 4.69 (7.9)	—	—	205, 6.05 (9.5)	—	—	—
(H ₂ O, pH = 7.2) ⁱ	267, 4.64 (9.7)	—	—	206.5, 6.00 ⁱ (9.8)	—	—	—
Stewart and Davidson ⁴³¹	Thymine ⁿ						
(H ₂ O, neutral pH)	273, 4.54 (0.19)			207, 5.99 (0.28)			
Clark and Tinoco ⁴¹⁷	Uracil						
(H ₂ O, pH = 7.0)	259, 4.79 (8.1)			202, 6.14 (8.8)	181, 6.85 ^k (15.5)		
(TMP) ^e	258, 4.81 (7.8)	—	—	203, 6.11 (8.2)	181, 6.85 ^k (11.8)	—	—
Clark <i>et al.</i> ⁴²²	Uracil						
(vapor)	244, 5.08	—	—	s205, 6.05	180, 6.90 ^k	—	—
Tanaka and Nagakura ⁴¹²	Thymine						
(H ₂ O, neutral pH; film) ^u	265, 4.68 (0.21)	—	—	205, 6.05 (0.31)	180, 6.90	163, 7.6	—
Miles <i>et al.</i> ⁴¹⁸	Uracil ^p						
(H ₂ O, pH = 7.0)	267, 4.64	~ 240, 5.17	~ 215, 5.77	196, 6.33	—	—	—
	262, 4.74 ^v (0.20)	~ 240, 5.17	~ 219, 5.65	196, 6.33 (0.30)	—	—	—
	Thymine ^{r, s}						
	272, 4.56	~ 242, 5.12	~ 217, 5.71	196, 6.33	—	—	—
	272, 4.56	~ 242, 5.12	~ 215, 5.77	197, 6.29	—	—	—

Yamada and Fukutome ⁴²⁸ (sublimed films) ^a	Uracil						
	268–264	—	—	205–203	178.5, 6.95	157, 7.90	144, 8.61
	4.63–4.70			6.05–8.11			
	Thymine						
	270–265	—	—	211, 5.88	176, 7.04	160, 7.75	144, 8.61
	4.59–4.68					(152, 8.16) ^o	
Crewe <i>et al.</i> ⁴³⁰ (energy losses) [†]	Uracil						
	~ 256, 4.85	—	—	~ 200, 6.2	~ 168 [†] , 7.4	—	~ 141, 8.8
	± 0.10			± 0.2	± 0.1		± 0.3
	Thymine						
	~ 261, 4.75	—	—	~ 210, 5.9	~ 166 [†] , 7.45	—	~ 143, 8.7
	± 0.10			± 0.2	± 0.10		± 0.3

^a The spectral data are described in the following way: the position of the maximum of absorption (or in circular dichroism spectrum) in nanometer units, transition energy in electron volts corresponding to the position of maximum. The oscillator strengths or $\epsilon \times 10^{-3}$ values are given in parentheses. The letter “s” signifies a shoulder.

^b From the spectrum of deoxycytidine.

^c Data for cytidine.

^d Uncertain assignment, probably band D.

^e TMP, trimethyl phosphate.

^f Estimated in the wavelength region longer than 180 nm.

^g From the CD spectrum of cytidine. The data in the second line quoted by Miles *et al.*⁴²⁰

^h Yamada and Fukutome⁴²⁸ have observed the next peak in the sublimed film spectrum of cytosine at 142 nm ($\Delta E = 8.73$ eV). This peak was poorly resolved and was not to be regarded as certainly established.

ⁱ Energy losses of sublimed films of pyrimidines. Crewe *et al.*⁴³⁰ have measured the higher energetic losses in the molecules (values in eV): cytosine 14.0 ± 0.5 , 22.0 ± 0.5 , uracil 14.8 ± 0.5 , 19.4 ± 0.5 , 26 ± 1 , thymine 15 ± 1 , 21.2 ± 0.5 , 27.5 ± 1.0 . They interpreted the ~ 14.0 – 15.0 eV loss as probably due to σ electron transitions, the broad energy loss at ~ 20 eV as a collective excitation of the σ plus π electrons, and the ~ 25 eV shoulder as due probably to the L_1 level of oxygen.

^j The C and D bands correspond to the E_{1u} (double degenerate, components E_{1ua} and E_{1ub}) band of benzene.

^k According to Clark and Tinoco⁴¹⁷ this band corresponds to the E_{1u} band of benzene.

^l From the spectrum of thymidine.

^m From the spectrum of uridine.

ⁿ From the spectrum of 1-methylthymine.

^o Two bands (poorly resolved).

^{p, r, s} From CD spectra of uridine, 5-methyluridine and thymidine, respectively.

[†] These energy losses correlate better with the F bands in the pyrimidines.

^u Bands 265 and 205 nm in H_2O at neutral pH, the next ones from the absorption spectrum of evaporated film on quartz plate.

^v Quoted by Miles *et al.*⁴²¹

pyrimidine nucleic acid bases can be classified into two groups, one restricted only to the excited states of the π -systems of the molecules [cytosines,^{14,104,144,156,159,173,177,178,188,189,201-204,206,208,213,235,259,420,421,433,434-436}, anionic^{104,156,159,437} and cationic^{104,213} forms of cytosines, uracils, and thymines,^{156,173,177,178,188,189,201-204,206,208,235,259,365,366,397,407,412,421,433,435,436,438-440} anions of uracils,^{158,440} adenine-thymine (uracil)^{184,186,441-443} and guanine-cytosine^{184,186,202,441-443} base pairs] and the second dealing with both their σ - and π -systems [cytosine,^{150,214,239,444} uracil and thymine,^{150,214,239,364,444} C-5-substituted uracil-1-malonic esters⁴⁴⁵ (EHT method), cytosine cation,⁴⁴⁴ and anion of uracil and thymine^{364,444}].

The first type of calculation was begun about ten years ago. On the contrary, the ($\sigma + \pi$)-electron calculations for excited states of the pyrimidines are scanty and have been published during the last four years. Only two papers, dealing with *ab initio* calculations on thymine and its anion³⁶⁴ and with the CNDO/2 CI calculations on the excited states of the nucleic acid bases,²³⁹ have reported the results of calculations for the $\pi \rightarrow \pi^*$ transitions as well as for the $\sigma \rightarrow \pi^*$, $n \rightarrow \pi^*$, or $\pi \rightarrow \sigma^*$ ones.

The papers reporting the π -SCF MO or CNDO/2 CI results for the transition energies of cytosine or uracil (or thymine) took usually as reference the experimental data (e.g., refs. 98, 413, 416, 417, 422) indicating in the UV region down to 180 nm the bands A (~ 4.5 eV), B (~ 5.3 eV), D (~ 6.1 eV), and E (~ 6.7 eV) in cytosine, and the bands A (~ 4.8 eV), D (~ 6.1 eV), and E (~ 6.9 eV) in uracil. The good agreement between the theoretical results and the experimental data, as reported in a number of papers^{14,104,173,188,189,201-203,207,365,412} dealing with the

⁴⁴³ H. Berthod, C. Giessner-Prettre, and A. Pullman, *C.R. Acad. Sci., Ser. D* **262**, 2657 (1966).

⁴⁴⁴ J. S. Kwiatkowski, *Acta Phys. Pol.* **29**, 573 (1966).

⁴⁴⁵ J. Ladik and K. Sundaram, *J. Mol. Spectrosc.* **29**, 146 (1969).

⁴³⁶ M. L. Bailey, *Theor. Chim. Acta* **16**, 307 (1972).

⁴³⁷ M. Berndt and J. S. Kwiatkowski, *Theor. Chim. Acta* **17**, 35 (1970).

⁴³⁸ H. Berthod, C. Giessner-Prettre, and A. Pullman, *Int. J. Quant. Chem.* **1**, 123 (1967).

⁴³⁹ H. DeVoe, *J. Phys. Chem.* **75**, 1509 (1971).

⁴⁴⁰ J. S. Kwiatkowski, presented at the 4th Int. Biophys. Cong., Moscow, August 7-14, 1972 (published as preprint No. 211 by the Inst. Phys., Nicholas Copernicus Univ. Toruń, Poland, 1972).

⁴⁴¹ V. A. Kuprievich, V. I. Danilov, and O. V. Shramko, *Mol. Biol.* **1**, 343 (1967).

⁴⁴² V. I. Danilov and N. V. Zheltovsky, *Theor. Chim. Acta* **19**, 384 (1970).

⁴⁴³ T. Miyata and S. Yomosa, *J. Phys. Soc. Jap.* **27**, 721 (1969).

⁴⁴⁴ W. Hug and I. Tinoco, *J. Amer. Chem. Soc.* **95**, 2803 (1973).

⁴⁴⁵ J. C. Nnadi, A. W. Peters, and S. Y. Wang, *J. Phys. Chem.* **77**, 482 (1973).

π -SCF MO calculations, is nevertheless questionable in view of the new assignment (see page 292) made by Miles *et al.*⁴¹⁸⁻⁴²¹ On the other hand, several π -SCF MO CI calculations^{177,178,235,259,433,436,438} had predicted the four $\pi \rightarrow \pi^*$ electronic transitions in cytosine and uracil (or thymine) in the UV region down to ~ 190 nm, before the work of Miles *et al.*^{418,419} (cf. Table XXIX). The transition energies calculated^{144,422} by means of the CNDO/2 CI method are less satisfactory in view of the new assignment. The calculated values of the singlet-singlet transition energies are sometimes about 1.2–1.5 eV higher than the corresponding experimental ones.

Only in a few papers has an attempt been made to interpret the electronic absorption spectra of anions and protonated cations of the bases. The absorption spectrum of cytosine in acidic as well as in alkaline aqueous solution differs from that in neutral.^{104,106} The first

TABLE XXIX

COMPARISON BETWEEN THEORETICAL (π -SCF MO CI) AND EXPERIMENTAL SPECTRAL DATA FOR THE LOWEST FOUR $\pi \rightarrow \pi^*$ TRANSITIONS OF CYTOSINE, URACIL, AND THYMINE

Theoretical			Experimental
Ref. 235, 433, 438 $^1\Delta E(f),^a \alpha^b$ (eV) (deg.)	$^3\Delta E^a$ (eV)	Ref. 418, 419 $^1\Delta E(f)^a$ (eV)	$^1\Delta E^{a,c}$ (eV)
Cytosine			
4.1 (0.1), +68	2.3	4.26 (0.10)	4.57
5.1 (0.1), -3		5.33 (0.37)	5.15
5.8 (0.4), -44		6.04 (1.11)	~ 5.68
6.3 (0.3), -50		6.62 (0.23)	6.36
Uracil			
4.8 (0.3), -9	2.0	4.81 (0.34)	4.74
5.4 (0.06), -9		5.49 (0.03)	~ 5.17
5.8 (0.2), +50		5.99 (0.46)	~ 5.65 –5.77
6.2 (0.6), -32		6.49 (0.81)	6.33
Thymine			
4.65 (0.4)	2.0	—	4.56
5.45 (0.1)		—	~ 5.12
5.6 (0.2)		—	~ 5.71 –5.77
6.2 (0.5)		—	6.29

^a $^1\Delta E$, $^3\Delta E$: singlet-singlet or singlet-triplet transition energies, oscillator strength (f) are given in parentheses.

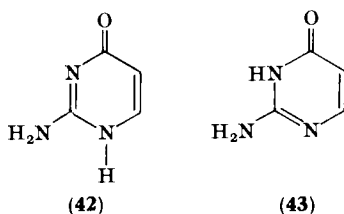
^b The angle α represents the polarization of the transition measured counterclockwise from the N-(1)–C-(4) axis.

^c Cf. Table XXVIII.

band of protonated cytosine ($\lambda_{\text{max}} = 275 \text{ nm}$) is shifted toward longer wavelengths and its intensity is increased in comparison to the corresponding band of the unprotonated compound. The second band appearing at $\sim 210 \text{ nm}$ has intensity similar to the first. The theoretical ΔE values^{104,213} agree very well with the values corresponding to the positions of the absorption bands of protonated cytosine. Morita and Nagakura¹⁰⁴ have also reproduced the relative shifts of the first and second bands of cytosine upon protonation. The agreement between the calculations of Morita and Nagakura¹⁰⁴ and the experiment is not unexpected since the spectra of both neutral and ionic forms of cytosine and isocytosine have been treated as references to evaluate core integrals of the method. The strong shift of the second band of cytosine toward shorter wavelengths has been only indicated as a trend by the computed transition energies by Denis and Gilbert.²¹³ The calculated ΔE -values (~ 4.4 and 5.5 eV) for cytosine anion^{104,437} are also in very good agreement with the experimental data¹⁰⁴ (~ 4.4 and 5.5 eV).

As mentioned in Section IV, uracil and thymine (as well as their several 5- and 6-derivatives) at pH 11–13 exist as an equilibrium mixture of two tautomeric forms corresponding to the dissociation of the N-1 or N-3 protons (forms **34** and **35**, respectively). These anions absorb at ~ 285 and $\sim 260 \text{ nm}$, respectively.^{324–328,338,345} Tentative calculations of the π -SCF MO CI type have been carried out for the UV spectra of the anions and for the dianion of uracil^{156,440} (cf. CNDO/2 CI calculations on this subject⁴⁴⁴). The calculations were performed for a number of structures having the negative charge located at the oxygen atom (or at the oxygens in the dianion). The structures **34a**, **34b**, and **35a**, **35b** are the resonance forms of the monoanions **34** and **35**, respectively. The calculations correctly interpret the fact that anion **34** absorbs at longer wavelengths than anion **35** and that the absorption of **34** is stronger than that of **35**. They deserve nevertheless some comment. In alkaline solution of uracil, a mixture of two tautomeric monoanions, **34** and **35**, appears, in which the negative charge is delocalized through the O-7---C-2---N-3---C-4---O-8 bond system of **35** or the O-7---C-2---N-1---C-6---C-5---C-4---O-8 system of **34** rather than being localized on the oxygen or nitrogen atoms of the anions. The *ab initio* LCAO SCF calculations on thymine and its anions³⁶⁴ indicate that when a proton is removed from a nitrogen of thymine to form **34** and **35**, a charge equivalent to about 3/4 of an electron migrates from nitrogen and is distributed over the molecule. This movement of charge occurs approximately equally through the σ and π electronic systems. The distributions of the charges in anions have been calculated for their ground state, and they are changed upon excitation. It is known that

analysis of the properties of the electronic absorption spectrum of an organic molecule gives primarily information on the π -electronic system of the molecule. Then the agreement between the calculated spectra of the canonical forms **34b** and **35b** and the experimental data indicates that the structures **34b** and **35b** describe correctly the behavior of the π -systems of anions **34** and **35**, respectively. The same conclusion can be drawn from the comparison of the UV spectra of the anions **35** and **34** with those of the molecules having π -electronic system similar to that of the anions. The spectroscopic features of the O^- substituent are very similar to those of the NH_2 group (cf. Section II) so that the π -systems of the cytosine tautomers **2**, **3** and those of the isocytosine tautomers **43**, **42** are models for the π -electronic structures of the anionic forms

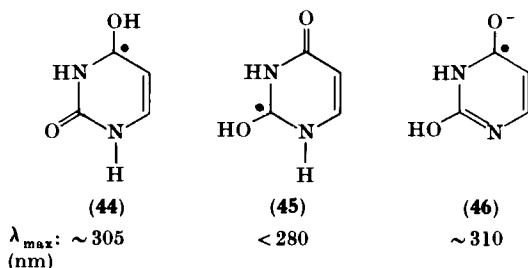


35a, **34a** and **34b**, **35b**, respectively. Thus the first absorption bands of the anions **34** ($\lambda_{\max} \approx 285$ nm) and **35** ($\lambda_{\max} \approx 260$ nm) are rather closer to those of the isocytosine tautomers¹⁰⁴ **43** ($\lambda_{\max} = 288$ nm) and **42** ($\lambda_{\max} \approx 259$ nm), respectively, than to the absorption bands of the cytosine tautomers¹⁰⁴ **3** ($\lambda_{\max} \approx 294$ nm) and **2** ($\lambda_{\max} \approx 267$ – 270 nm), respectively.

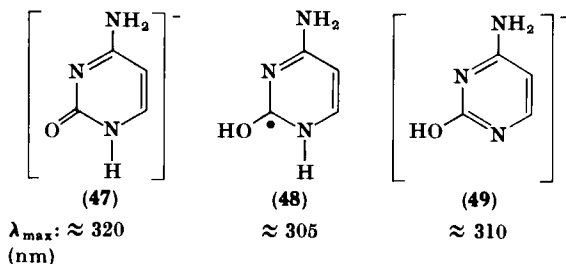
The π -SCF MO CI method has also been used⁴⁴⁶ to interpret spectral transitions of a series of possible intermediates in the reaction of uracil and cytosine with the solvated electrons e_{aq}^- , produced by radiolysis of water. Experimentally this reaction has been investigated by Hayon,⁴⁴⁷ who used the technique of flash radiolysis. Hayon measured the optical-absorption spectra of the transient species in the UV range to obtain information on the site of attack of e_{aq}^- on the pyrimidine base. At pH ~ 5.0 the solvated electrons react with the pyrimidine molecules mainly at the C-2 and C-4 carbonyls, and the intermediates are rapidly protonated to give the corresponding ketyl radicals. For uracil Hayon found two absorption maxima (at 305 and < 280 nm) at pH 5.1 and one peak at 310 nm at pH 11.7. In this last case, on ionization of one of the chromophores the ketyl radical anion of the other nondissociated carbonyl is formed. Several species, **44**, **45**, **46**, have been suggested by

⁴⁴⁶ A. Grimison and M. K. Eberhardt, *J. Phys. Chem.* **77**, 1673 (1973).

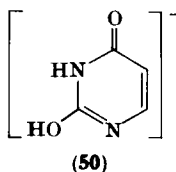
⁴⁴⁷ E. Hayon, *J. Chem. Phys.* **51**, 4881 (1969).



Hayon⁴⁴⁷ to absorb in this UV region. Similar measurements have been made for a number derivatives of uracil (5,6-dihydro, 1-, 3-, and 6-methyl, 1,3-dimethyl-, and 5-aminouracil, orotic acid, barbituric and isobarbituric acids; also see similar measurements⁴⁴⁸ on 5-bromouracil and its *N*-methyl derivatives), thymine itself and its derivatives (5,6-dihydro, 2-methylthymine). In the case of cytosine, Hayon⁴⁴⁷ has very tentatively suggested that species **47** and **48** are obtained on pulse radiolysis of the solution at pH 5.5, and **49** at pH 13.3.



Grimison and Eberhardt⁴⁴⁶ carried out calculations of the transition energies and oscillator strengths for the uracil and cytosine radical anions mentioned above and for **50**, the uracil lactim radical anion, using a specially designed Pariser-Parr-Pople type approximation, including configuration interaction. Comparing calculated



with experimental spectra, Grimison and Eberhardt confirmed the previous assignments of Hayon for cytosine radical anions, but made new assignments in the case of uracil. They suggested that, on pulse radiolysis of aqueous uracil, species **44** was formed at neutral pH

⁴⁴⁸ E. Hayon, *J. Chem. Phys.* **51**, 4893 (1969).

(Hayon's suggestion: **44**, **45**) and species **50** in alkaline solution (Hayon's suggestion: **46**). The calculation (the spectra as well as the INDO calculation⁴⁴⁶ of electron densities of uracil and cytosine radical anion) suggested that the solvated electron reacts with uracil and cytosine by addition to the lowest unoccupied molecular orbital, followed at neutral pH by protonation to form the C-4 ketyl radical of uracil and the C-2 ketyl radical of cytosine. The calculation on transition energies presented in ref. 446 cannot be treated as evidence that the species above is the one formed on pulse radiolysis of aqueous solutions of the pyrimidines.

B. THE DIRECTION OF THE TRANSITION MOMENTS

Experimentally, the direction of a transition moment in a molecule can be evaluated by four methods: (i) polarized spectra of single crystals, (ii) fluorescence or phosphorescence polarization, (iii) spectra of molecules embedded in stretched films, and (iv) spectra of molecules oriented by external fields. Only relative directions of the transition moment can be determined by means of the last three methods, whereas the polarized spectra of single crystals give the absolute direction of the moments if the crystal structure is known. The first method has been applied to the study of the electronic structure and spectra of several pyrimidine bases of nucleic acid.^{408,409,425,426,431,449-451} In many cases, however, the direction of the transition moments of the bands could not be fixed since the crystal structures were not yet analyzed. The directions of the moments obtained from the observed dichroic ratios are tabulated in Table XXX. The values for the first and several $\pi \rightarrow \pi^*$ bands of uracils, thymines, and cytosines are rather scattered, particularly if one compare the results of Tanaka and Tanaka^{450,451} with those of other authors. It was pointed out⁴⁵¹ that the probable error in the determination of the direction of the first transition in uracil and thymine is of about $\pm 14^\circ$, and -38° and -86° were proposed as the average values of the directions of the first and the next (C, D?) transition moment in thymine. The angle between the directions of these two transition moments of 48° , is however, in disagreement with the determination of Fucaloro and Forster⁴³² by the stretched-film method. On the other hand, the results of the stretched-film spectra and of fluorescence polarization measurements provide, in general, the same qualitative information. Fucaloro and Forster⁴³²

⁴⁴⁹ R. F. Stewart and N. Davidson, *Biopolym. Symp.* **1**, 465 (1964).

⁴⁵⁰ M. Tanaka and J. Tanaka, *Bull. Chem. Soc. Jap.* **44**, 672 (1971).

⁴⁵¹ M. Tanaka and J. Tanaka, *Bull. Chem. Soc. Jap.* **44**, 938 (1971).

TABLE XXX

DIRECTION^a OF THE TRANSITION MOMENTS IN THE PYRIMIDINE NUCLEIC ACID BASES AND THEIR DERIVATIVES

1. Determined from the observed dichroic ratios					
Compound	$\pi \rightarrow \pi^*$ band		$\pi \rightarrow \pi^*$ band		References
	λ_{\max} (nm)	α (degrees)	λ_{\max} (nm)	α (degrees)	
Uracil	(A) 255	— 19 or — 23 (— 16 or — 26)	—	—	451
1-Me-uracil	275.5	0 ± 1 or $+7 \pm 1$	(C, D?)	$(\perp_1)^b$ (C, D?)	409
1-Et-6-CH ₃ -uracil	265	— 45 or + 60 (— 48 or + 55)	220	— 35 or + 80	451
Thymine anhydrate	255	— 52 or — 66 (— 50 or — 68)	220	— 55 or — 63	451
Thymine monohydrate	265	— 35 or — 78 (— 24 or — 81)	220	— 43 or — 76	451
1-Me-thymine		— 19 or + 14		$(\perp_1)^b$	408, 431, 449
1-Me-thymine	270	— 84 or + 77 (— 80 or + 70)	235	— 87 or + 84	451
Calcium thymidilate	280	— 79 or + 87	220	— 82 or + 88 (+ 86)	451
Cytosine monohydrate	~ 270	+ 14 or + 10 (± 1)	238	— 5 \pm 3	426
Cytosine monohydrate	265	— 25 or + 80	220	— 45 or — 80	450
1-Me-cytosine	265	between + 9 and — 11	230	— 1 \pm 10	425
Cytidine	272	— 15 or + 75	230	— 20 or — 90	450

2. Relative directions of the transition moment determined from polarized fluorescence (pol. fl.) or stretched film spectra (st.f.sp.)					
Compound	$\pi \rightarrow \pi^*$ band		$\pi \rightarrow \pi^*$ band		References
	λ_{\max} (nm)	Rel. pol. ^c (degrees)	λ_{\max} (nm)	Rel. pol. ^c (degrees)	
Cytosine (st.f.sp.)	~ 240 (B)	1.6	< 205 (C, D?)	95.4	432
5-Me-cytosine (pol. fl.)	~ 240 (B)	40 ± 15	—	—	425
Uracil (st.f.sp.)	(C, D?)	97.7 or 3.3	—	—	432
Thymine (st.f.sp.)	(C, D?)	95.8 or 1.4	—	—	432

^a Measured counterclockwise from the direction N(1) \rightarrow C(4) according to the convention of DeVoe and Tinoco.²³³ The assignment of the bands is given in parentheses.

^b Approximately perpendicular to the lowest (first) $\pi \rightarrow \pi^*$ transition.

^c Rel. pol, relative polarization, i.e., relative to the first absorption band.

have found essential agreement between the results of the two methods wherever information from fluorescence polarization is available (cytosine, adenine). We ought to keep in mind also that the interactions in the crystal may lead to erroneous results.^{439,452}

Calculating the optical properties of 1-methyluracil crystal by an all-order classical oscillator theory, DeVoe⁴³⁹ has shown that the direction of the molecular transition moment could not be reliably determined from crystal polarization ratios. Two other methods, (ii) and (iii), seem also to give only qualitative information on the directions of the transition moment because, for instance, when determining the angle between the moments of two transitions from polarization, the depolarization effects are usually omitted. Recently, the directions of the transition moments to the lowest excited singlet states of uracil and thymine with respect to the directions of their ground state dipole moments have been determined from the influence of an electric field on the light absorption of the molecules in solution.⁴⁰⁵ The determination of the direction of the transition moment is possible by making use of the results on the orientation of the ground state dipole moment in the molecular framework; when this moment is not known, Seibold and Labhart⁴⁰⁵ use the experimental directions of the transition moments^{408,409,431} to evaluate the direction of the dipole moments in the ground and first excited singlet state (Cf. Section V).

Although the experimental data are only approximate and although theoretical directions of the transition moment have also a limited significance, we shall briefly compare the experimental and calculated results.

The π -SCF MO CI and CNDO/2 CI calculations on uracil predict the first $\pi \rightarrow \pi^*$ transition to be polarized within $+5^\circ$ to -9° of the N-1 \rightarrow C-4 direction in good agreement with the experimental determination by Eaton and Lewis⁴⁰⁹ on 1-methyluracil. Comparing this last result with that of Stewart and Davidson,^{408,431,449} we see that the further 5-methyl substitution of 1-methyluracil, to form 1-methylthymine, causes a rotation of the transition moment direction of about 19° or 26° . The π -SCF MO CI calculations on thymine³⁶⁶ which explicitly include the methyl group predict a rotation of 15° . The predicted rotation is in agreement with the experimental results, insofar as the 1-methyl group may be neglected. This seems to be justified as the theory predicts that the substitution of 1-methyl group of uracil²⁰⁸ causes a negligible change of the direction of the moment, from -9° to -7° .

The next intense absorption (bands C and D) in 1-methyluracil (~ 220

⁴⁵² H. H. Chen and L. B. Clark, *J. Chem. Phys.* **51**, 1862 (1969).

nm in the crystalline state or ~ 207 nm in an aqueous solution) is polarized approximately perpendicular to the lowest $\pi \rightarrow \pi^*$ transition.⁴⁰⁹ This is also the case in 1-methylthymine,^{408,431,449} and stretched film spectra of both uracil and thymine also indicate that the A and C(?), D(?) $\pi \rightarrow \pi^*$ bands may have their transitions polarized approximately perpendicular to each other.

In the case of cytosine the comparison between experiment and theory for the directions of the transition moments is less satisfactory. Thus, the results of a recent CNDO/2 CI calculation on cytosine are in accordance with the experimental evidence^{425,426} suggesting the polarization of the first transition to be of $+9^\circ$ to $+14^\circ$ (theor. $\alpha_1 = +18^\circ$) and the direction of the second transition to be nearly but not exactly parallel to that of the first transition. On the other hand, the π -SCF MO CI calculations give α_1 50 – 70° in agreement with the data of Tanaka and Tanaka.⁴⁵⁰ These calculations, however indicate a large angle between the first and second transition moments. On the other hand, the π -SCF MO CI calculations on 5-methylcytosine²⁰⁸ give satisfactory results for the angle between the first and second transition moments (theor.²⁰⁸: 61° , exp.⁴²⁵: $\sim 40 \pm 15^\circ$).

C. TRIPLET STATES

Precise experimental location of the triplet states in the pyrimidine bases of the nucleic acids is very rare. Their identification was long rendered difficult by the very low phosphorescence of these compounds,⁴⁵³ which is observable only at relatively high concentrations and at low temperature⁴⁵⁴ (77°K). On the basis of the phosphorescence studies of the isolated pyrimidines¹¹³ and of the energy transfer in dinucleotides^{454,455} (see, however, ref. 456) where the occurrence of the triplet-triplet energy transfer in these dinucleotides was not observed), Hélène *et al.*⁴⁵⁴ suggested that the first triplets of the pyrimidines were lower than those of the purines, and that uracil had the lowest triplet among the four bases. Rahn *et al.*⁴⁵⁷ showed by electron spin resonance and phosphorescence measurements that the ultraviolet excited triplet

⁴⁵³ R. Bersohn and I. Isenberg, *J. Chem. Phys.* **40**, 3175 (1964).

⁴⁵⁴ C. Hélène, P. Douzou, and M. Michelson, *Biochim. Biophys. Acta* **109**, 261 (1965).

⁴⁵⁵ C. Hélène, P. Douzou, and M. Michelson, *Proc. Nat. Acad. Sci. U.S.* **55**, 376 (1966).

⁴⁵⁶ M. Guéron, R. G. Shulman, and J. Eisinger, *Proc. Nat. Acad. Sci. U.S.* **56**, 814 (1966).

⁴⁵⁷ R. O. Rahn, R. G. Shulman, and J. W. Longworth, *J. Chem. Phys.* **45**, 2955 (1966).

state in DNA and poly(dAT) was located in the thymine residues. They first suggested that the DNA triplet was to be found on the thymine anion formed by the transfer of the thymine N-3 proton across the adenine-thymine hydrogen bond, but later Lamola *et al.*⁴⁵⁸ concluded that the DNA triplet was that of neutral thymine rather than that of the thymine anion. It should be noted that Lamola *et al.* could not eliminate the possibility of the lactim tautomer, which they did not study for lack of suitable models. Guéron *et al.*⁴⁵⁹ measured the phosphorescence spectra of nucleotides at 77°K and concluded that the order of decreasing energies was U^- , C, T^- , T for their triplets. (Here U, C, T, G, and A stand for a nucleotide containing the uracil, cytosine, thymine, guanine, or adenine base, respectively.) This order of energies of pyrimidine nucleotide triplets compare well with the order of cytosine > thymine (uracil) calculated by several authors. But in general there is poor agreement between calculated positions of the lowest triplets of the nucleic acid bases [adenine > guanine > cytosine > thymine (uracil)] and the experimental order of the nucleotide triplets (C > G > A > T). A possible explanation of this discrepancy is that the calculations were for the bases and the measurement for the ribosyl derivatives.

As the singlet-triplet absorption is unknown, the triplet energy can only be estimated from the blue edge of the phosphorescence^{459,460}; this may, however, give rise to appreciable errors. The energies of the lowest vibronic levels of the lowest triplet states as determined from the blue edges of the phosphorescence^{459,460} are 3.46 and 3.26 eV above the ground state for cytosine and thymine nucleotides, respectively.^{460a} Similarly, the lowest vibronic levels of the first excited singlet states of these nucleotides are located at 4.18 and 4.23 eV above their ground state, respectively, so the singlet-triplet separation is of the order of 0.72 and 0.97 eV for cytosine and thymine mononucleotides, respectively. These last values are considerably smaller than the calculated data which range from 1.5 to 2.5 and 2.4 to 3.7 eV for cytosine and thymine nucleotides, respectively. It is worth noting that the observed singlet-triplet splittings for nucleotides are also considerably smaller

⁴⁵⁸ A. A. Lamola, N. Guéron, T. Yamane, J. Eisinger, and R. G. Shulman, *J. Chem. Phys.* **47**, 2210 (1967).

⁴⁵⁹ M. Guéron, J. Eisinger, and R. G. Shulman, *J. Chem. Phys.* **47**, 4077 (1967).

⁴⁶⁰ J. Eisinger, *Photochem. Photobiol.* **7**, 597 (1968).

^{460a} The energies of the transition from the ground to the first excited triplet state ($\pi \rightarrow \pi^*$ type) of 5-bromo and 5-iodo-uracil have been measured⁴⁶¹ from the singlet-triplet absorption spectra of crystalline samples of these uracils using the phosphorescence excitation technique. They are equal to 3.10 and 3.06 eV, respectively.

TABLE XXXI

COMPARISON OF THE COMPUTED AND OBSERVED^{253,458} TRIPLET STATE ELECTRON SPIN RESONANCE SPIN HAMILTONIAN PARAMETERS FOR THYMINE^a

Wave function used		D ($\times 10^3 \text{ cm}^{-1}$)		E ($\times 10^3 \text{ cm}^{-1}$)	
		Calc.	Exp.	Calc.	Exp.
Neutral molecule	<i>Ab initio</i> ³⁶⁴	-169	± 200	-14	± 10
	π -HMO ^{176,462}	-180			
	π -SCF MO ⁴⁶³	-142		-17	
	π -SCF MO CI ⁴⁶³	-282			
Anion	<i>Ab initio</i> ³⁶⁴	-161	± 196	-8	± 10
	π -HMO ^{176,462}	-180			
Anion	<i>Ab initio</i> ³⁶⁴	-108	± 166	-28	?

^a Corresponding values for uracil have been calculated⁴⁶³ to be equal to 169, 295 for D ($\times 10^3 \text{ cm}^{-1}$) using the π -SCF MO or π -SCF MO CI wavefunction, and to 17 for E ($\times 10^3 \text{ cm}^{-1}$) using the π -SCF MO wavefunction.

than the corresponding splittings for benzene-like or naphthalene-like molecules.

In a few papers an attempt has been made to interpret quantum-mechanically the zero-field splitting parameters, which have been determined from the analysis of the electron spin resonance spectra on the triplet state of the pyrimidine bases.

The ESR spin Hamiltonian parameters have been calculated using π -HMO and π -SCF MO coefficients in the molecular orbitals^{176,462,463} as well as those from nonempirical wavefunctions.³⁶⁴ It may be seen that, in general, calculated values are in good agreement with experimental data (Table XXXI).

D. ELECTRONIC FACTORS IN THE PHOTODIMERIZATION OF PYRIMIDINES

Quantum-mechanical methods have been used to calculate the electronic characteristics of the excited state of the pyrimidines. These characteristics can be found in the following papers: (a) *charge distributions* q_i —for π -HMO calculations, see refs., 1, 464–466; π -SCF MO (without or with CI) and/or *open-shell* π -SCF MO calculations on cytosine,^{174,176,177,203,206,207,466} uracil,^{174,176,177,203,206,207,407,466} thymine,^{174,203,206,207,366,466} guanine-cytosine,^{175,184,441,442} adenine-thymine

⁴⁶¹ W. Rothman and D. R. Kearns, *Photochem. Photobiol.* **6**, 775 (1967).

⁴⁶² A. Pullman and E. Kochanski, *Int. J. Quant. Chem.* **1s**, 251 (1967).

⁴⁶³ E. Kochanski and A. Pullman, *Int. J. Quant. Chem.* **3**, 1055 (1969).

⁴⁶⁴ M. J. Mantione and B. Pullman, *Biochim. Biophys. Acta* **91**, 387 (1964).

⁴⁶⁵ J. Ladik, *J. Theor. Biol.* **6**, 201 (1964).

⁴⁶⁶ B. Pullman, *Photochem. Photobiol.* **7**, 525 (1968).

(uracil),^{175,184,441,442} q_5 and q_6 in cytosine, uracil, thymine,^{187-189,467} 5-methylcytosine, 6-azathymine, orotic acid, 6-methyl-, 5-amino- and 5-nitrouracil¹⁸⁷⁻¹⁸⁹; for dipole moment of uracil, see ref. 407; *CNDO/2* *CI* calculations on cytosine, uracil, thymine (including their dipole moments),²³⁹ the change of q_i at nitrogens and oxygens on excitation of uracil and cytosine.¹⁵⁰

(b) *Bond orders* P_{ij} —for π -HMO calculations, see refs. 1, 464, 466; π -SCF MO (without or with CI) and/or *open-shell* π -SCF MO calculations on cytosine, uracil, thymine,^{174,176,466,467} guanine-cytosine and adenine-thymine (uracil),^{441,442} P_{56} in cytosine, uracil, thymine, 5-methylcytosine, 6-azathymine, orotic acid, 6-methyl-, 5-amino-, and 5-nitrouracil¹⁸⁷⁻¹⁸⁹; *CNDO/2* *CI* calculations of nondiagonal elements of the density matrix at the C(5)–C(6) bond of uracil.²³⁹

(c) *The density of the uncoupled electrons (or spin density)* ρ_i —for π -HMO calculations, see ref. 431; π -SCF MO (without or with CI) and/or *open-shell* π -SCF MO, π -UHF calculations on cytosine and uracil,^{176,177,206,235,438,466} thymine,^{206,235,366,438,466} 5-methylcytosine,⁴⁶² guanine-cytosine and adenine-thymine⁴⁴²; ρ_i at C-5 and C-6 of cytosine, uracil, thymine,^{187-189,467} 5-methylcytosine, 6-azathymine, orotic acid, 6-methyl-, 5-amino-, and 5-nitrouracil¹⁸⁷⁻¹⁸⁹; *CNDO/2* (without or with CI) calculations on cytosine and thymine,^{214,239} uracil.²³⁹

Attempts have been made to correlate these characteristics with the rate of photodimerization of a series of pyrimidine bases.^{467a} Among these characteristics, two appeared to be particularly important for the photodimerization problem (for review see ref. 466), namely the density of the uncoupled electrons (or spin density) ρ_i at C-5 and C-6 and the change of the C(5)–C(6) bond order P_{56} upon excitation. The proposal that the high concentration of spin density on the C(5)–C(6) bond as well as its low bond order in the excited states were factors responsible for the case of photodimerization was stated about ten years ago.^{464,471} The first calculations, within the framework of the π -HMO approximation, showed the following findings: (i) The concentration of uncoupled

⁴⁶⁷ V. I. Danilov, *Photochem. Photobiol.* **6**, 233 (1967).

^{467a} In a few papers⁴⁶⁸⁻⁴⁷⁰ an attempt has been made to interpret the photodimerization of the pyrimidine bases by evaluating the energy of interaction between the monomers through perturbation theory.

⁴⁶⁸ C. Nagata, Y. Imamura, M. Tagashira, M. Kodama, and N. Fukuda, *J. Theor. Biol.* **9**, 357 (1965).

⁴⁶⁹ R. M. Sayre, J. P. Harlos, and R. Rein, in "Molecular Orbital Studies in Chemical Pharmacology" (L. B. Kier, ed.) p. 207. Springer-Verlag, Berlin and New York, 1970.

⁴⁷⁰ J. Bertrán, *Theor. Chim. Acta* **25**, 372 (1972).

⁴⁷¹ B. Pullman and M.-J. Mantione, *Biochim. Biophys. Acta* **95**, 668 (1965).

electrons occurs at the C-5 and C-6 in the first excited states of the pyrimidines undergoing photodimerization (in 5-nitro- and 2-thiothymine, which do not dimerize, the maximum concentration of the lone electrons is at the exocyclic substituent, NO_2 or S, respectively). (ii) The pyrimidines undergoing photodimerization show a striking decrease of the P_{56} value upon excitation. The yield of photodimerization correlates well with the total concentration of uncoupled electrons at the C(5)–C(6) bond as well as with the variation of the P_{56} value upon excitation.

An important problem concerns the nature of the first excited state actually involved in the photodimerization reaction (the lowest excited singlet or triplet states). The simple π -HMO method does not distinguish between the excited singlet and triplet state. Its results concern the "first excited state" and cannot be correlated precisely with the different multiplicities. For such a correlation, the more refined approximations of the molecular orbital method, which eliminate spin degeneracy, must be used.

At this point, it is worthwhile to point out that the problem is also complicated from the experimental point of view. A number of investigators favor the triplet state as that involved in the photodimerization reaction of pyrimidines (e.g., refs. 472–483). On the other hand, Eisinger and Shulman⁴⁸⁴ adopted a more balanced viewpoint by suggesting that although the triplet state is the precursor of the dimer in liquid solution, the dimer formed in frozen aqueous solution originates most likely from the excited singlet state. Lamola and Mittal⁴⁷⁵ have shown that photodimerization of uracil in acetonitrile and in water proceeded only in part through the triplet state. More recently it was also shown that in concentrated solutions the pyrimidine dimers are

⁴⁷² B. Beukers and W. Berends, *Biochim. Biophys. Acta* **49**, 181 (1961).

⁴⁷³ E. Sztumpf and D. Shugar, *Photochem. Photobiol.* **4**, 719 (1965).

⁴⁷⁴ A. Haug and P. Douzou, *Z. Naturforsch. B* **20**, 509 (1965).

⁴⁷⁵ A. A. Lamola and J. P. Mittal, *Science* **154**, 1560 (1966).

⁴⁷⁶ A. A. Lamola and T. Yamane, *Proc. Nat. Acad. Sci. U.S.*, **58**, 443 (1967).

⁴⁷⁷ E. Sztumpf-Kulikowska, D. Shugar, and J. W. Boag, *Photochem. Photobiol.* **6**, 41 (1967).

⁴⁷⁸ M. Charlier and C. Hélène, *Photochem. Photobiol.* **6**, 501 (1967).

⁴⁷⁹ C. L. Greenstock, I. H. Brown, J. W. Hunt, and H. E. Johns, *Biochem. Biophys. Res. Commun.* **27**, 431 (1967).

⁴⁸⁰ J. G. Burr, B. R. Gordon, and E. H. Park, *Photochem. Photobiol.* **8**, 73 (1968).

⁴⁸¹ C. Greenstock and H. E. Johns, *Biochem. Biophys. Res. Commun.* **30**, 21 (1968).

⁴⁸² D. W. Whillans, M. H. Herbert, J. W. Hunt, and H. E. Johns, *Biochem. Biophys. Res. Commun.* **36**, 912 (1969).

⁴⁸³ D. W. Whillans and H. E. Johns, *J. Amer. Chem. Soc.* **93**, 1358 (1971).

⁴⁸⁴ J. Eisinger and R. G. Shulman, *Proc. Nat. Acad. Sci. U.S.* **58**, 895 (1967).

formed within ground state stacked complexes via a singlet excimer precursor.⁴⁸⁵⁻⁴⁸⁹

The results of the refined MO calculations (π -SCF MO without and with CI, open-shell π -SCF MO, π -UHF, or CNDO/2 CI methods) differ depending on the approximations used. In some cases, the π -SCF MO CI method gives results quite similar for both states to those obtained by π -HMO method for the "first excited state." These results [spin densities, bond orders P_{56} , and free valences on the C(5)-C(6) bond] all correlate with the greater tendency to photodimerization of uracil and thymine compared with cytosine and do not indicate which of the excited states is involved in the reaction. On the other hand, Danilov *et al.*^{187-189,467} using the π -SCF MO CI as well as the open-shell π -SCF MO methods have calculated that the bond order of the C(5)-C(6) bond in the first triplet of a series of pyrimidines is lower than in the first excited singlets of the corresponding molecules, and have concluded that dimerization of the bases occurs via the triplet state. They divided the pyrimidines into three groups: the pyrimidines which are known to be easily dimerizable (uracil, 6-methyluracil, thymine, orotic acid—for these molecules the P_{56} values in their T_1 state are of the order of 0.09–0.12), those which dimerize not so easily (5-aminouracil, cytosine, 5-methylcytosine— $P_{56} \approx 0.13$ –0.17), and the bases which do not dimerize at all or only with considerable difficulty (2-thiothymine, $P_{56} = 0.31$; isocytosine, $P_{56} = 0.39$; and 5-nitrouracil). The relative distribution of the bases within groups leads sometimes to only limited agreement with available experimental data. For instance, as the $P_{56} = 0.085$ in T_1 of uracil is lower than $P_{56} = 0.106$ in T_1 of thymine, uracil should dimerize more easily than thymine, a conclusion in disagreement with experiment.⁴⁹⁰

VII. Tautomerism, Electronic Structures, and Spectra of Rare Pyrimidine Bases of the Nucleic Acids

A. GEOMETRICES

X-Ray results are available for the molecular structures of nearly all rare pyrimidine constituents of the nucleic acids except for isothiocytosine. Thio analogs of uracil exist in the tautomeric form of the **32** type;

⁴⁸⁵ I. H. Brown and H. E. Johns, *Photochem. Photobiol.* **8**, 273 (1968).

⁴⁸⁶ G. I. Fisher and H. E. Johns, *Photochem. Photobiol.* **11**, 429 (1970).

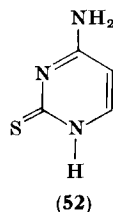
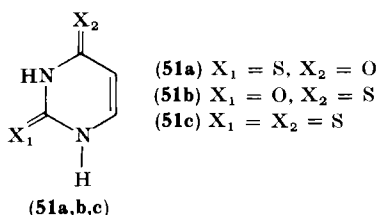
⁴⁸⁷ H. Morrison and R. Kleopfer, *J. Amer. Chem. Soc.* **90**, 5037 (1968).

⁴⁸⁸ R. Lisewski and K. L. Wierzchowski, *Chem. Commun.*, 348 (1969).

⁴⁸⁹ R. Lisewski and K. L. Wierzchowski, *Mol. Photochem.* **3**, 231 (1971).

⁴⁹⁰ A. Śmietanowska and D. Shugar, *Bull. Acad. Pol. Sci. Cl. II* **9**, 375 (1961).

i.e., they are the lactam-thiones (**51a,b**) or dithiones (**51c**). The C–S bond lengths are of the order of 1.65–1.67 Å, which means that they have a high double-bond character^{7,491,492} (shorter than a C–S single bond of 1.82 Å, closer to a double bond of 1.56 Å). The C–O bonds (1.22–1.24 Å) have also a strong double bond character.⁷ The two C–S bond lengths of 2,4-dithiouracil differ by about 0.01–0.04 Å, with the C(4)–S(8) bond being the longer one. An examination of the crystallographic data for 2-thiocytosine⁴⁹³ shows that the molecule has the amine-thione form **52**, by analogy to cytosine, with the hydrogen at N-1.



In general, thiouracils and 2-thiocytosine are planar, but close examination of the least-squares plane through the six atoms of the pyrimidine ring in 2-thiocytidine dihydrate⁴⁹¹ shows that the ring atoms C-2 and N-3 are significantly displaced to opposite sides of the plane. The exocyclic atoms S-7 and N-8 show also marked displacements to the same side of the ring.

An interesting feature was discovered by Sharma and co-workers^{494,495} in the crystal structure of isocytosine. Two tautomers of isocytosine (**42** and **43**) exist in an exact 1:1 ratio in the crystal. The tautomers are hydrogen-bonded to each other in a manner analogous to that proposed by Watson and Crick^{496,497} for the guanine-cytosine pair in DNA. It is worth underlining that the base pair of isocytosine was not obtained by expedient cocrystallization of the two components. It seems therefore probable that both forms **42** and **43** of isocytosine are of approximately equal stability and are present in comparable amounts in solution.

⁴⁹¹ G. H.-Y. Lin, M. Sundaralingam, and S. K. Arora, *J. Amer. Chem. Soc.* **93**, 1235 (1971).

⁴⁹² M. Sundaralingam, in "The Purines—Theory and Experiment" (E. D. Bergmann and B. Pullman, eds.), p. 73. Israel Acad. Sci. Humanities, Jerusalem (distributed by Academic Press, New York), 1972.

⁴⁹³ S. Furberg and L. H. Jensen, *Acta Crystallogr. Sect. B* **26**, 1260 (1970).

⁴⁹⁴ J. F. McConnell, B. D. Sharma, and R. E. Marsh, *Nature (London)* **203**, 399 (1964).

⁴⁹⁵ B. D. Sharma and J. F. McConnell, *Acta Crystallogr.* **19**, 797 (1965).

⁴⁹⁶ J. D. Watson and F. H. C. Crick, *Nature (London)* **171**, 737 (1953).

⁴⁹⁷ J. D. Watson and F. H. C. Crick, *Nature (London)* **171**, 964 (1953).

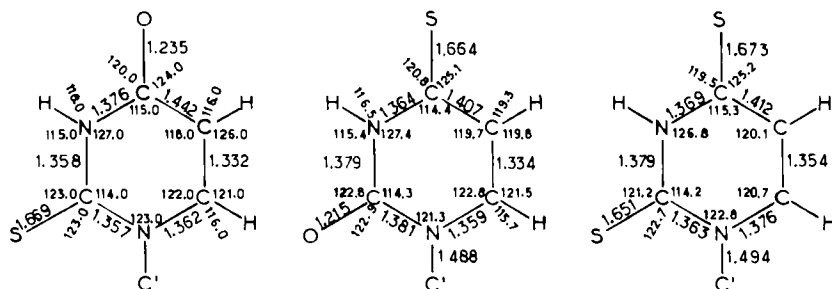


FIG. 18. The bond distances (Å) and bond angles (degrees) in 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil, obtained by averaging of results from crystal structure containing the bases: 2-thiouracil⁴⁹⁸ (cf. ref. 492), 4-thiouracil (1-methyl-thiouracil: 9-methyl-adenine,⁴⁹⁹ 4-thiouridine hydrate,⁵⁰⁰ 1, β -D-arabino-furanosyl-4-thiouracil,⁵⁰¹ 3'-O-acetyl-4-thiothymidine^{502,503}), 2,4-dithiouracil (parent molecule,⁵⁰⁴ 2,4-dithiouridine monohydrate^{505,506}).

Figures 18 and 19 collect the averaged geometrical parameters for thiouracils and thiocytosine. The geometrical structures of the two isocytosine tautomers can be found in the paper by Sharma and McConnell.⁴⁹⁵

Sulfur substitution changes the geometry of the base somewhat.^{506a} The changes of bond lengths in cytosine and the three thiouracils caused by substitution of oxygen by sulfur are collected in Table XXXII, together with the corresponding negative differences of the π -bond orders calculated by the π -HMO method.⁵⁰⁷ Italicized figures refer to the bonds adjacent to the carbon substituted by sulfur. The substitution of sulfur for oxygen causes a shortening of the distances of the bonds adjacent to the substituted carbon. There is, however, no linear

⁴⁹⁸ D. Tsernoglou, Ph. D. Thesis, Yale Univ., New Haven, 1966 (quoted by Sundaralingam⁴⁹²).

⁴⁹⁹ W. Saenger and D. Suck, *J. Mol. Biol.* **60**, 87 (1971).

⁵⁰⁰ W. Saenger and K. H. Scheit, *J. Mol. Biol.* **50**, 153 (1970).

⁵⁰¹ W. Saenger, *J. Amer. Chem. Soc.* **94**, 621 (1972).

⁵⁰² W. Saenger, D. Suck and K. H. Scheit, *FEBS Lett.* **5**, 262 (1969).

⁵⁰³ W. Saenger and D. Suck, *Acta Crystallogr., Sect. B* **27**, 2105 (1971).

⁵⁰⁴ E. Shefter and H. G. Mautner, *J. Amer. Chem. Soc.* **89**, 1249 (1967).

⁵⁰⁵ G. H.-Y. Lin and M. Sundaralingam, *Acta Crystallogr., Sect. B* **27**, 961 (1971).

⁵⁰⁶ W. Saenger and D. Suck, *Acta Crystallogr., Sect. B* **27**, 1178 (1971).

^{506a} The π -bond orders calculated by different methods for the ground state of minor pyrimidine bases can be found in the following papers: π -HMO calculations on 2-thio, 4-thio, and 2,4-dithiouracil,⁵⁰⁷ 5- and 6-azaisocytosine,⁵⁰⁸ also see^{1,509}; π -SCF MO calculations on isocytosine,¹⁰⁴ P₅₆ for isocytosine and 2-thiothymine.¹⁸⁷⁻¹⁸⁹

⁵⁰⁷ H. Mautner and G. Bergson, *Acta Chem. Scand.* **17**, 1694 (1963).

TABLE XXXII
INFLUENCE OF THE SUBSTITUTION OF SULFUR FOR OXYGEN IN CYTOSINE AND URACIL ON THE BOND DISTANCES^a
(Å) AND π -HMO BOND ORDERS^{507,b}

	Bond ^c					
	N(1)-C(2)	C(2)-N(3)	N(3)-C(4)	C(4)-C(5)	C(5)-C(6)	C(6)-(N(1)
Cytosine \rightarrow 2-thiocytosine	-0.021	-0.015	0.010	-0.015	-0.004	0.003
Uracil \rightarrow 2-thiouracil	-0.018	-0.017	-0.010	0.006	-0.010	-0.014
	(-0.003)	(0.008)	(-0.001)	(0.001)	(0.007)	(-0.009)
Uracil \rightarrow 4-thiouracil	0.006	0.004	-0.022	-0.029	-0.008	-0.015
	(0.001)	(-0.001)	(0.019)	(-0.038)	(0.003)	(0.024)
Uracil \rightarrow 2,4-dithiouracil	-0.012	0.004	-0.017	-0.024	0.012	0.000
	(0.000)	(0.005)	(0.016)	(-0.036)	(0.008)	(0.011)

^a The differences between the experimental bond distances of sulfur bases (Figs. 18 and 19), and those of the parent molecules.⁷

^b The differences between calculated π -bond orders of uracil and of its thio analogs (numbers in parentheses).

^c Italicized figures refer to the bonds adjacent to the carbon substituted by sulfur.

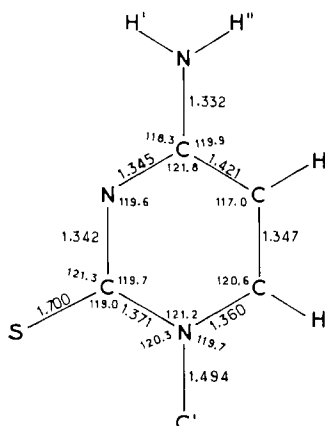


FIG. 19. The bond distances (Å) and bond angles (degrees) in 2-thiocytosine ring, obtained by averaging the results from 2-thiocytosine⁴⁹³ and 2-thiocytidine dihydrate.⁴⁹¹

correlation between the calculated values given in Table XXXII and the corresponding experimental data.

B. TAUTOMERISM OF MINOR PYRIMIDINE BASES OF THE NUCLEIC ACIDS IN SOLUTION

The X-ray crystallographic studies show that thiouracils and 2-thiocytosine exists in the crystalline state in forms **51** and **52**, respectively, and that isocytosine exists as a mixture of two amine-lactam forms, **42** and **43**. Several experimental studies on these pyrimidines in solution confirm the conclusions from the crystal. However, studies on the tautomerism of the minor pyrimidine bases are few. In a number of cases the conclusions about the dominant structures are intuitive rather than proved. We present the essential experimental data on the structure of the minor pyrimidine bases.

1. *Isocytosine*

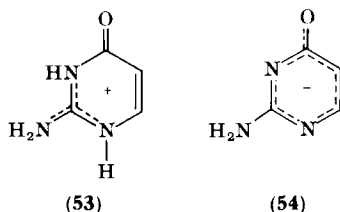
IR studies^{38,40,510} suggested that this molecule exists in the solid state as well as in solution in the amine-lactam form **42** and **43**, or as a mixture of the two forms. These studies were not able to distinguish

⁵⁰⁸ J. Piřha, P. Fiedler, and J. Gut, *Collect. Czech. Chem. Commun.* **31**, 1864 (1966).

⁵⁰⁹ B. Pullman and A. Pullman, "Results of Quantum Mechanical Calculations of the Electronic Structure of Biochemicals." Inst. Biol. Phys.-Chim. Univ. Paris, 1960.

⁵¹⁰ I. A. Brownlie, *J. Chem. Soc.*, 3062 (1950).

which tautomer predominates. A number of spectroscopic studies have been carried out for isocytosine using the electronic absorption spectra,^{38,104,112,113,511,512} special attention being paid to their tautomeric forms. They indicate that isocytosine exists predominantly as the form **43** in ethanol and in ethyl ether, but in aqueous solution two tautomeric forms, **42** and **43**, coexist in comparable amounts.^{104,112,113,512} Hélène and Douzou¹¹² concluded that tautomer **42** is more stable by ~ 1 kcal/mole than tautomer **43** in aqueous solution. Morita and Nagakura¹⁰⁴ determined the corresponding energy differences and the entropy change to be 1.3 kcal/mole and 4.7 cal/mole degree, respectively, on the basis of the temperature dependence of the absorption spectrum of the molecule. The ionic forms (cation and anion) of isocytosine have been shown to have the structures **53** and **54**, respectively, by UV^{104,511} and NMR^{63,65} spectroscopic studies. The NMR study showed⁶⁵ also that the dication of this molecule has a structure similar to **53** with a



further proton added at the oxygen. UV studies on isocytosine (as well as data from ionization constants) are particularly well documented, and they indicate that both tautomers **42** and **43** exist in the crystalline state as well as in aqueous solution in comparable amounts.

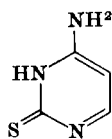
5-Aza and 6-aza substitution cause a shift in the tautomeric equilibrium of isocytosine. In 5-azaisocytosine, form **42** predominates over form **43** by a factor of $\sim 10^2$, whereas in 6-azaisocytosine, form **43** is more stable than form **42**.⁵⁰⁸

2. Thiocytosine and Isothiocytosine

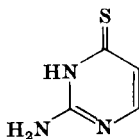
Information on the tautomerism in thio analogs of cytosine and isocytosine is scanty. After comparing the UV spectra and ionization constants of these molecules with those of their methylated derivatives, Brown and Teitei⁵¹¹ suggested that thiocytosine exists as a mixture of **52** and **55** in aqueous solution, and isothiocytosine exists rather in form **56**. As the 1-methyl derivative of isocytosine was not available, the latter conclusion is uncertain. In fact, the π -SCF MO CI calculations

⁵¹¹ D. J. Brown and T. Teitei, *Aust. J. Chem.* **18**, 559 (1965).

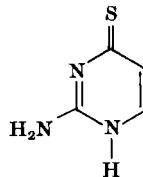
⁵¹² C. Hélène and P. Douzou, *C.R. Acad. Sci.* **259**, 4387 (1964).



(55)



(56)



(57)

(see further) suggest that the UV spectrum of isothiocytosine contains overlapping spectra of both tautomers **56** and **57**.

In several experimental papers dealing with the properties of 2-thiocytosine, usually the amine-thione form is assumed for the pyrimidine residue (e.g., ref. 80). Mass spectral fragmentation schemes of a number of *s*-triazines have been presented⁵¹³ where 5-azathiocytosine has the amine-thione form.

Similarities may be seen, comparing the UV spectra of anions of thiocytosine and isothiocytosine with those of 4-amino-2-methylthiopyrimidine and 2-amino-4-methylthiopyrimidine.⁵¹² The spectra of anionic forms are shifted toward longer wavelengths compared to those of methylthio compounds, but the shapes of the bands are similar. As the S⁻ substituent is a stronger electron donor than the SMe (cf. ref. 514), the UV spectra suggests structures with negative charges at sulfur for the anions.

3. 2-Thio-, 4-Thio-, and 2,4-Dithiouracil

The predominant form of 2-thiouracil has been shown⁵¹⁵ to be **51a** in acid and neutral aqueous solutions, by comparing the UV spectra of several derivatives and their *pK* values. With further increase in pH, two equilibria have been demonstrated spectrophotometrically, considered first to give the monoanion with the negative charge localized on sulfur, and next the dianion with negative charges localized on sulfur and oxygen.

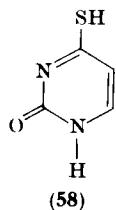
In the case of 4-thiouracil it is possible to compare its UV spectrum with that of 1,6-dimethyl-4-methylthiouracil.⁵¹⁶ As the spectra are different from each other, 4-thiouracil is supposed not to exist in form **58**. The comparison of the UV spectrum of 4-thiouracil with those of some 5-methoxy-4-thiouracil nucleosides³⁶² indicates that the pyrimidine residues of the latter have the same structure as that of 4-thiouracil

⁵¹³ J. de Lannoy and R. Nasielski-Hinkens, *Bull. Soc. Chim. Belges* **81**, 587 (1972).

⁵¹⁴ J. S. Kwiatkowski, M. Berndt, and J. Fabian, *Acta Phys. Pol.* **A38**, 365 (1970).

⁵¹⁵ D. Shugar and J. J. Fox, *Bull. Soc. Chim. Belges* **61**, 293 (1952).

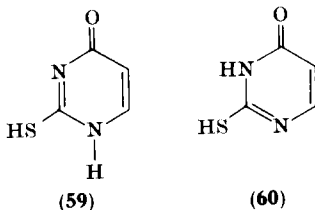
⁵¹⁶ L. Lang (ed.), "Absorption Spectra in the Ultraviolet and Visible Region." Akad. Kiado, Budapest.



itself. The same conclusion can be drawn from the similarities between the UV spectra of 4-thiouridines, 4-thiothymidines, and the parent base.^{517,518}

The UV spectrum of 2,4-dithiouracil has been measured (e.g., refs. 507, 519). It is not possible, however, to compare it with those of model compounds having fixed structures because of lack of experimental data.

The UV and IR spectra of a number of 3-alkyl-6-methyl-2-thiouracils have been measured.⁵²⁰ The IR spectra indicate the lactam-thione form **51a** with no other tautomers. Tautomerism was also ruled out on the basis of similar studies on 2-thiouracil.⁵²¹ The differences in the IR spectra of 6-methyl-2-thiouracil and its 2-methylthio derivative⁵¹⁰ indicate that 2-thiouracil does not have the thiol form **59** or **60**. On the



other hand, the NMR spectrum in deuterated dimethyl sulfoxide of 2-thiouracil³²⁸ has been attributed to the keto-thiol form (**60**).

4. Quantum-Mechanical Studies

Quantum-mechanical studies on the tautomeric stabilities of the rare pyrimidine bases are very scarce. Tentative CNDO/2 calculations have been carried out^{156,440} on the energies of some of them. They showed that in thiouracils the most stable form in each case is form **51**. In 2-thiocytosine, two forms, **52** and **55**, are nearly equivalent (form **52** is more stable than **55** by ~4 kcal/mole), and isothiocytosine form **56**

⁵¹⁷ R. Wightmann and A. Holý, *Collect. Czech. Chem. Commun.* **38**, 1381 (1973).

⁵¹⁸ S. Irie, F. Egami and Y. Inoue, *J. Amer. Chem. Soc.* **91**, 1582 (1969).

⁵¹⁹ C. Hélène and G. Lancelot, *J. Chim. Phys.* **67**, 189 (1970).

⁵²⁰ K. A. Nuridzhanyan and V. G. Blinova, *Zh. Prikl. Spektrosk.* **12**, 513 (1970).

⁵²¹ G. V. Kazakova, *Zh. Obshch. Khim.* **38**, 1601 (1968).

prevails over form **57** by ~ 14 kcal/mole. Tentative CNDO/2 calculations performed during the preparation of this article by ourselves indicate that form **43** of isocytosine is more stable than **42** by 4–5 kcal/mole.

C. DISTRIBUTION OF ELECTRON DENSITIES

The π charge densities for a few minor pyrimidine bases have been calculated by means of the π -HMO method [q_N of the ring in 2-thiouracil, 2-thio, 4-thio, and 2,4-dithio-6-azauracil,⁵²² 2-thio, 4-thio, and 2,4-dithiouracil⁵²³ (the last paper includes also q_N 's calculated by π -HMO + σ -Del Re method); q_t for 6-azaisocytosine,⁵²² 2-thio, 4-thio, and 2,4-dithiouracil⁵⁰⁷; cf. also refs. 1, 509] and by π -SCF MO method (q_N of the ring of isocytosine,²⁰⁰ q_5 and q_6 of isocytosine and 2-thiothymine,^{187–189} q_t of the forms **42** and **43** and the lactam-imine of isocytosine¹⁰⁴). These results are not reproduced here. We list, however, the more significant results of CNDO/2 (without d-orbitals) calculations (Fig. 20). It may be

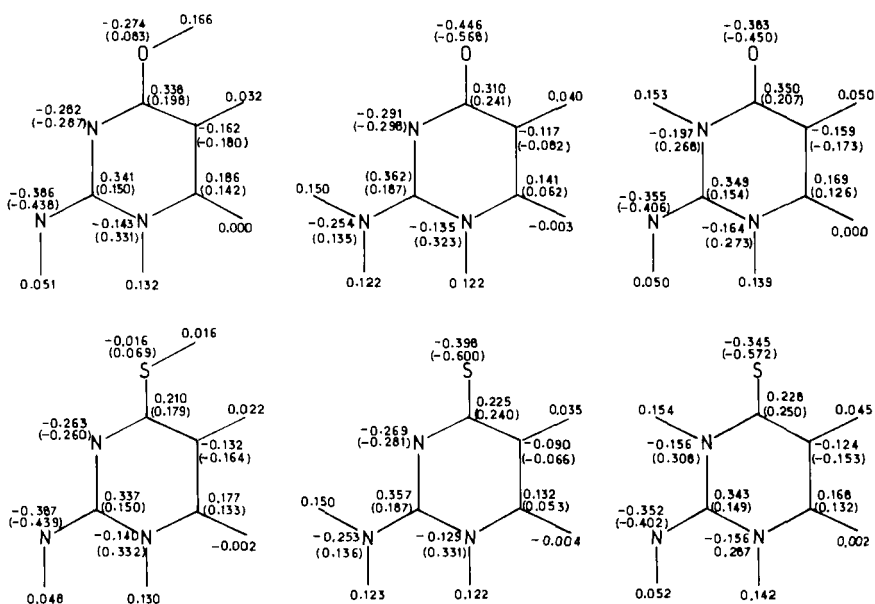


Fig. 20a. See caption on facing page.

⁵²² J. Piřha and S. Vařířková, *Collect. Czech. Chem. Commun.* **30**, 1792 (1965).

^{522a} For recent results of CNDO/2 (with d-orbitals) calculations on thiouracils see M. Geller, A. Pohorille, and A. Jaworski, *Biochim. Biophys. Acta* **331**, 1 (1973).

⁵²³ H. Berthod and A. Pullman, *C.R. Acad. Sci., Ser. C* **262**, 76 (1966).

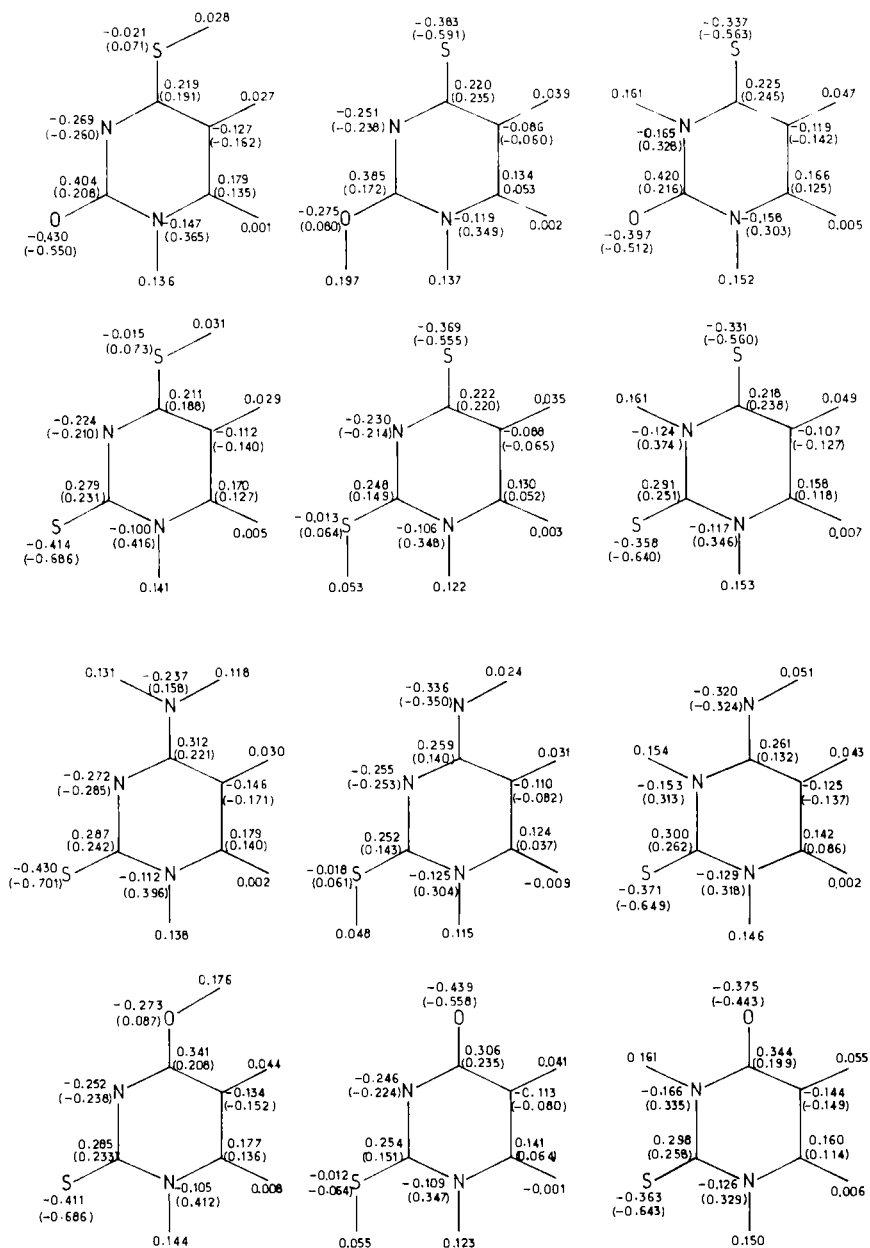


FIG. 20. Net total electronic charge in minor pyrimidine bases of the nucleic acids calculated by the CNDO/2 method. The numbers in parentheses indicate π -charges.

seen by comparing with Figs. 3–5 and 10–13 that the charge distributions in pyrimidines are considerably modified when an oxygen atom is replaced by a sulfur atom.^{522a}

As concerns the dipole moments of these pyrimidines, the CNDO/2 (without d-orbitals) method seems to give somewhat too high values for the sulfur compounds. In this case the simpler methods give more satisfactory results. For instance, the calculated dipole moments of thiouracils by Berthod and Pullman⁵²³ by means of the π -HMO + σ -Del Re procedure are in very good agreement with the available experimental data⁵²⁴ (2-thiouracil: $\mu_{\text{calc.}}$ 4.04 D, $\mu_{\text{exp.}}$ 4.21 D; 4-thiouracil: $\mu_{\text{calc.}}$ 4.53 D, $\mu_{\text{exp.}}$ 4.47 D; 2,4-dithiouracil: $\mu_{\text{calc.}}$ 4.59 D, $\mu_{\text{exp.}}$ 4.67 D).

D. MOLECULAR ORBITAL ENERGIES: ELECTRON-DONATING AND ELECTRON-ACCEPTING PROPERTIES

The values of the ionization potentials of a few minor pyrimidine bases were estimated from the "charge transfer" spectra²⁵⁵ (Table XXXIII). These values compare well with the ionization potentials calculated by means of the π -SCF MO method.¹⁵⁶ However, the relative order of the ionization potentials given by the calculations (π -SCF MO and CNDO/2 methods, Tables XXXIII and XXXIV)—thiocytosine

TABLE XXXIII
THEORETICAL (π -SCF MO)¹⁵⁶ AND EXPERIMENTAL
(FROM CT SPECTRA)²⁵⁵ IONIZATION POTENTIALS OF
RARE PYRIMIDINE BASES

Compound, tautomer	Theoretical ^a (eV)	Experimental (eV)
Isoctosine, 42	8.45	—
43	8.22	—
Thiocytosine, 52	7.51	—
55	7.56	7.83
Isothiocytosine, 56	7.62	—
57	7.38	—
2-Thiouracil, 51a	8.61	8.25
6-NH ₂ -2-thiouracil	—	7.90
4-Thiouracil, 51b	8.44	—
2,4-Dithiouracil, 51c	8.57	8.38

^a "Corrected" ionization potential relative to benzene (see Section III, E).

⁵²⁴ W. C. Schneider and I. F. Halverstadt, *J. Amer. Chem. Soc.* **70**, 2626 (1942).

\lesssim 2,4-dithiouracil < 2-thiouracil—differ somewhat from the experimental order—thiocytosine < 2-thiouracil < 2,4-dithiouracil. For all tautomers of the rare pyrimidine bases, the CNDO/2 calculations predict that both the highest occupied and lowest empty molecular orbitals are of the π -type (Table XXXIV).

E. ELECTRONIC ABSORPTION SPECTRA

Singlet-singlet transition energies of the minor pyrimidine bases have been calculated in a few papers (π -SCF MO CI calculations: isocytosine^{104,156,188,189} and its anion^{104,437} and cation,¹⁰⁴ 2-thiothymine,^{188,189} 2-*S*-methylcytosine and 4-*S*-methylisocytosine and anions of thiocytosine and isothiocytosine,⁵¹⁴ 2-thio, 4-thio, 2,4-dithiouracil, thiocytosine, and isothiocytosine^{156,440} and several methyl derivatives of rare pyrimidines and their anions¹⁵⁶).

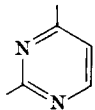
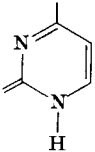
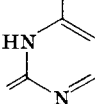
The calculated transition energies for both tautomers **42** and **43** of isocytosine are in good agreement with experimental.¹⁰⁴ The UV spectrum of the anionic form of the compound is also correctly interpreted by the calculations.^{104,437}

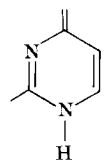
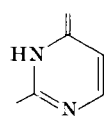
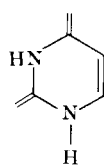
When an oxygen atom in uracil or cytosine (isocytosine) is replaced by sulfur, the electronic properties of the molecules are changed substantially. The spectrum of 2-thiouracil⁵¹⁵ is thus different from that of uracil.⁴¹⁷ At first sight, the first two bands in uracil are shifted toward longer wavelengths when an oxygen at position 2 is substituted by sulfur, and the intensity of the bands is increased. In fact, the first absorption band in 2-thiouracil has an inflection on the long-wave side covering a $\pi \rightarrow \pi^*$ transition. The nature of the absorption bands of uracil itself is complicated (cf. Section VI,A).

In the case of 4-thiouracil, the predicted position of the near UV band^{156,440} is in moderate agreement with experiment. The difference in energy is about 0.5 eV. Experimental evidence shows that the C=S bond in the molecule is much more polar than the corresponding bond in 2-thiouracil. When this fact is included in the calculation,¹⁵⁶ the position of the first band is shifted toward longer wavelengths, while the transition energies corresponding to the absorption at 250 nm are unchanged. The UV spectrum of 2,4-dithiouracil is also different from that of uracil, and the calculations^{156,440} are in good agreement with experiment.

The positions of the absorption bands of thiocytosine and isothiocytosine are given in Table XXXV together with the predicted values. The CNDO/2 calculation shows¹⁵⁶ that tautomers **52** and **55** of thiocytosine have similar energies, and the π -SCF MO CI calculations for

TABLE XXXIV
 ENERGIES^a OF THE LOWEST EMPTY (LEMO) AND THREE HIGHEST OCCUPIED HOMO MOLECULAR ORBITALS
 IN MINOR PYRIMIDINE BASES OF THE NUCLEIC ACIDS CALCULATED BY CNDO/2 METHOD¹⁵⁶

		Isocytosine	Thiocytosine	Isothiocytosine	2-Thiouracil	4-Thiouracil	2,4-Dithiouracil
	LEMO:	3.56	3.75	3.54	3.37	3.24	3.38
	HOMO:	-11.83	-11.26	-11.29	-11.60	-11.69	-11.30
		-12.72 σ	-12.20 σ	-11.98 σ	-12.51 σ	-12.29 σ	-12.02
		-13.75	-12.44	-12.33	-13.20 σ	-13.38	-12.22 σ
	LEMO:	2.10	2.07	2.12	1.56	1.92	1.57
	HOMO:	-10.07	-8.94	-9.92	-9.25	-10.82	-9.12
		-12.58 σ	-9.15 σ	-11.90 σ	-9.51 σ	-11.90 σ	-9.38 σ
		-13.18 σ	-12.06 σ	-12.37	-12.41 σ	-12.49	-12.29 σ
	LEMO:	2.21	2.01	2.22	1.57	1.99	1.61
	HOMO:	-9.95	-8.96	-9.77	-9.23	-10.62	-9.09
		-12.45 σ	-9.30 σ	-12.12 σ	-9.57 σ	-11.98 σ	-9.43 σ
		-13.49 σ	-12.23 σ	-13.03 σ	-12.55 σ	-13.35	-12.33 σ

	LEMO:	2.83	2.75	2.36	2.49	1.93	2.20
	HOMO:	-10.02	-9.53	-8.51	-10.12	-8.76	-8.74
		-11.20 σ	-11.07 σ	-8.64 σ	-11.34 σ	-8.96 σ	-8.87 σ
		-12.98 σ	-12.73	-11.36 σ	-12.95	-11.67 σ	-11.60 σ
	LEMO:	2.62	2.63	2.32	2.19	1.88	2.07
	HOMO:	-10.34	-9.68	-8.90	-10.48	-9.18	-9.12
		-11.98 σ	-11.77 σ	-9.19 σ	-12.08 σ	-9.47 σ	-9.39 σ
		-13.13 σ	-13.16	-12.05 σ	-13.20 σ	-12.38 σ	-12.24 σ
	LEMO:	2.45	2.36	1.59	2.04	1.40	1.25
	HOMO:	-11.45	-10.38	-9.81	-10.53	-9.94	-10.05
		-12.10	-10.40 σ	-9.88 σ	-10.56 σ	-10.04 σ	-10.14 σ
		-12.83 σ	-11.18	-11.79	-12.06	-12.73	-10.63

^a All values are given in electron volts. Unlabeled orbitals are π levels. The energies of the most stable tautomers of the molecules are italicized.

these two tautomers (Table XXXV) also place the absorption bands close to each other. Thus the absorption spectra of these two tautomers are very similar to each other and strongly overlapping, so that it does

TABLE XXXV
COMPARISON BETWEEN EXPERIMENTAL⁵¹¹ AND CALCULATED^{156,440}
(π -SCF MO CI) SPECTRA OF THIOCYTOSINE AND ISOTHIOCYTOSINE

Theoretical ^a				Experimental ^a	
ΔE (eV)	f	ΔE (eV)	f	ΔE (eV)	log ϵ
Thiocytosine					
52		55			
3.22	0.10	3.19	0.23	—	—
4.65	0.62	4.58	0.48	4.61	4.26
5.17	0.61	5.19	0.42	5.12	4.26
5.83	0.01	6.19	0.20	—	—
Isothiocytosine					
57		56			
3.76	0.07	3.64	0.34	3.62	4.11
4.11	0.78	—	—	~ 4.13 ^b	—
—	—	4.41	0.49	4.80	3.65
5.20	0.21	5.48	0.13	~ 5.30	3.67
6.03	0.49	5.98	0.40	—	—

^a ΔE , transition energy; f , oscillator strength; ϵ , molar extinction coefficient.

^b Slope of the absorption band.

not seem possible to resolve the experimental spectrum into contributions from each tautomer.

In the case of isothiocytosine the tautomers **56** and **57** are more stable than the other possibilities, the former being more stable by ~ 14 kcal/mole than the latter. The calculations performed for tautomer **56**, (see Table XXXV) predict, in general, correctly the positions of the absorption bands, although for the second band the predicted position is in poorer agreement with experiment than the other bands. If we assume that in solution isothiocytosine exists as a mixture of two tautomers, **56** and **57**, with the former predominating, we explain the slope of the absorption curve in the 300 nm region.

VIII. Miscellaneous Properties

A. INNER SHELLS (ESCA)

Barber and Clark⁵²⁵⁻⁵²⁷ have described the results of the X-ray photoelectron spectroscopy of the binding energies of the molecular core electrons in adenine, cytosine, and thymine. Since the experimental core ionization energies were almost linearly related to the orbital energies from nonempirical SCF LCAO MO calculations,²¹⁹ they assigned the photoelectron peaks to ionization of the corresponding carbon or nitrogen atoms. They pointed out⁵²⁵ that *a priori* there is no reason to expect the linear relationship between molecular core binding energies (as measured by photoelectron spectroscopy or calculated by SCF LCAO MO method) and the gross atomic electron populations derived from a Mulliken population analysis. In fact, if each molecule is considered separately, an almost linear relationship exists between the C_{1s} binding energy and the gross atomic populations on carbons but not for the nitrogen atom. Later Van der Avoird⁵²⁸ has shown that the linear relationship was restored if the experimental binding energies are corrected for the effect of the Madelung potential due to the other atoms in the molecule^{529,530} considered as point charges.

A comparison of the binding energies with the net charges calculated by the CNDO/2 method (Table XXXVI) has shown⁵³¹ a linear relationship between these two quantities for the carbon atoms of the nucleic acid bases (except for the C-5 carbons of cytosine and thymine) as well as for the nitrogens. However, these last relationships are less satisfactory than the previous ones.⁵²⁸

Other attempts to correlate experimental binding energies with molecular-charge distributions have been made. Kato *et al.*⁵³² have derived a correlation formula between the chemical shift of the inner-shell electron of a molecule and the charges both on the ionized and other atoms (cf. ref. 529). Very recently Ishida *et al.*⁵³³ reported an

⁵²⁵ N. Barber and D. T. Clark, *Chem. Commun.*, 22 (1970).

⁵²⁶ M. Barber and D. T. Clark, *Chem. Commun.*, 23 (1970).

⁵²⁷ M. Barber and D. T. Clark, *Chem. Commun.*, 24 (1970).

⁵²⁸ A. Van der Avoird, *J. Chem. Soc., Chem. Commun.*, 727 (1970).

⁵²⁹ U. Gelius, B. Roos and P. Siegbahn, *Chem. Phys. Lett.* **4**, 471 (1970).

⁵³⁰ K. Siegbahn, C. Nordling, A. Fahlman, R. Nordberg, K. Hamrin, J. Hedman, G. Johansson, T. Bergmark, S. E. Karlsson, I. Lindgren, and B. Lindberg, *Nova Acta Regiae Soc. Sci. Upsal.* [4], 20 (1970).

⁵³¹ A. Imamura, H. Fujita, and C. Nagata, *J. Amer. Chem. Soc.* **94**, 6287 (1972).

⁵³² H. Kato, K. A. Ishida, H. Nakatsuji, and T. Yonezawa, *Bull. Chem. Soc. Jap.* **44**, 2587 (1971).

⁵³³ A. T. Ishida, H. Kato, H. Nakatsuji, and T. Yonezawa, *Bull. Chem. Soc. Jap.* **45**, 1574 (1972).

TABLE XXXVI
COMPARISON BETWEEN EXPERIMENTAL BINDING ENERGIES AND THEORETICAL QUANTITIES
FOR THE NUCLEIC ACID BASES

Atom	Experimental 1s binding energy (eV), ± 0.3 eV	Negative value (eV) of orbital energy (<i>ab initio</i> ²¹⁹)	Net gross atomic population (<i>ab initio</i> ²¹⁹)	Net charges (CNDO/2 ⁵³¹)	Theoretical chemical shift ⁵³² (eV)	Theoretical 1s binding energy ^{532,a} (eV)
Cytosine						
N-1	401.4	429.28	-0.597	-0.16	-1.33	-174.13
N-8	400.5	428.79	-0.719	-0.23	-1.90	-174.13
N-3	399.6	428.35	-0.461	-0.34	-5.87	-177.74
C-2	289.4	315.09	+0.637	+0.44	4.22	-58.13
C-4	287.9	314.55	+0.363	+0.33	4.75	-58.28
C-6	286.5	313.73	-0.013	+0.19	3.29	-59.30
C-5	285.4	311.55	-0.480	-0.17	-0.28	-60.34

Thymine						
N-1	402.1	431.87	-0.708	-0.19	—	-173.75
N-3	401.1	431.07	-0.715	-0.25	—	-174.25
C-2	289.9	316.69	+0.771	+0.43	—	-56.81
C-4	288.5	315.07	+0.562	+0.36	—	-57.62
C-6	286.6	313.28	+0.019	+0.15	—	-59.51
C-5	285.8	310.87	-0.144	-0.12	—	-60.60
C (methyl)	285.1	309.81	-0.820	+0.01	—	-61.19
Adenine						
N-9	400.9	432.55	-0.670	-0.10	-1.24	-174.23
N-10	399.6	429.70	-0.811	-0.24	-4.73	-175.55
N-7	399.5	429.66	-0.425	-0.25	-2.67	-177.06
N-3	399.1	429.21	-0.501	-0.25	-4.68	-177.09
N-1	398.6	429.14	-0.511	-0.27	-5.98	-177.13
C-6	287.8	314.43	+0.405	+0.26	3.04	-59.05
C-4	286.6	313.91	+0.344	+0.21	2.40	-59.16
C-8	286.2	313.37	+0.155	+0.18	1.88	-60.14
C-2	285.7	313.00	+0.178	+0.21	1.63	-60.75
C-3	284.7	311.91	-0.003	-0.05	-0.44	-59.89

^a Using different approximations for the carbon and nitrogen atoms (see text).

application of this formula to the correlation of the observed binding energies^{526,527} with the calculated chemical shifts in adenine and cytosine. The relationship between these two quantities is nearly linear, in particular for the carbons 1s electrons of adenine. Imamura *et al.*⁵³¹ have derived a formula for the calculation of the chemical shift including the charge redistribution effect within the CNDO/2 scheme and have applied it to the chemical shifts of the carbon and nitrogen atoms in adenine, thymine, and cytosine. A satisfactory correlation between experimental and theoretical chemical shifts was obtained when the theoretical values for the carbon and nitrogen atoms were calculated with different approximations. In the case of the carbon atoms the shifts correlated satisfactorily with the binding energies calculated without modification of the parameters included in the CNDO/2 treatment (except for the core charge of the ionized atom, which was increased by 1 owing to the ionization of an inner-shell electron). However for the nitrogen chemical shifts, they have used modified parameters (the parameters of the oxygen atom were used for the ionized nitrogen atom). The authors have attempted to justify the calculation of the chemical shifts for the carbon and nitrogen atoms by different approximations. The first approximation of the method should be applicable for molecules with a relatively small charge redistribution upon ionization, while the second is suitable for molecules with a relatively large charge redistribution. The charge redistributions in adenine upon ionization of the carbon or the nitrogen inner-shell electrons calculated by the use of these two approximations were given as an example to show how the different parametrizations could be rationalized.

B. NMR AND NQR SPECTROSCOPIC STUDIES

In Sections II and IV we have described the application of NMR and NQR spectroscopy to the determination of the localization of mobile protons of the pyrimidine bases and for the prediction of the tautomeric structures of these molecules. Here, we shall describe the application of these spectroscopies to the elucidation of the electronic structures of the most stable tautomeric forms of the bases.

Four characteristic parameters can be measured on the NMR absorption curves: (i) intensity, (ii) position of the signal (usually given relative to a standard and called the chemical shift), (iii) width, usually measured at half peak height, and (iv) coupling constant characterizing the division of a signal into a multiplet. Quantum-

mechanical methods have been applied essentially only to the interpretation of the second and fourth parameters.

The *proton magnetic resonance* (PMR or ^1H MR) spectra of the pyrimidine bases as well as of their derivatives and nucleosides have been studied abundantly. The chemical shifts ($\delta_{1\text{H}}$), spin-spin coupling constants, as well as the shifts in PMR spectra of the bases induced by substituents, have been measured and discussed. The PMR spectra have also been used to investigate the interaction between metals and the pyrimidine bases (in particular, see ref. 69) as well as for the study of the association of the bases and of the restricted rotation about the exocyclic N-C bond in cytosines (cf. Section III,C). Unfortunately, the quantum-mechanical interpretation of the PMR data of the pyrimidine bases is scanty. Veillard and Pullman,⁵³⁴ and Veillard⁵³⁵ attempted to correlate the $\delta_{1\text{H}}$ values with the π -charges on the atoms carrying the protons. They calculated the so-called "corrected" $\delta_{1\text{H}}$ values using McWeeny's modification of London's MO theory of π -electron ring currents and plotted these values against the π -charges. Almost linear correlations were observed between these quantities in the series of N-heterocyclic molecules (including cytosines, uracils, thymines, and 2-thiouracil), provided that the individual protons (H-1, H-3, H-5, or H-6) were considered separately. Veillard⁵³⁵ has also shown that the proton spin-spin coupling constants $J_{\text{H-5-H-6}}$ of cytosine, 2-thiouracil and uracil were proportional to the π -bond order of the C(5)-C(6) bonds in the molecules. The high-field shifts observed for H-5 correlate with the high charge densities calculated at this position for all the pyrimidine bases under consideration. Very recently, Giessner-Prettre and Pullman^{536,537} have performed PCILO and INDO calculations of both the short and long range proton-proton coupling constants in a number of purine and pyrimidine nucleosides [among which are uridine, α - and β -pseudouridine, 6-azauridine, 6-methyluridine, thymidine (2'-deoxy) cytidine, and dihydrouracil] as a function of the conformational characteristics of these compounds. Comparing theoretical with experimental data the authors concluded that an equilibrium existed in solution between several conformers of the nucleosides.

The ^{13}C *magnetic resonance* spectra have been reported for naturally occurring nucleotides⁵³⁸, nucleosides,^{79-81,539} and uracil, thymine, 5-

⁵³⁴ A. Veillard, and B. Pullman, *C.R. Acad. Sci.* **253**, 2418 (1961).

⁵³⁵ A. Veillard, *J. Chim. Phys.*, 1056 (1962).

⁵³⁶ C. Giessner-Prettre and B. Pullman, *J. Theor. Biol.* **40**, 441 (1973).

⁵³⁷ C. Giessner-Prettre and B. Pullman, *Int. J. Quant. Chem.* **7s**, 295 (1973).

⁵³⁸ D. E. Dorman and J. D. Roberts, *Proc. Nat. Acad. Sci. U.S.* **65**, 19 (1970).

⁵³⁹ M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, *J. Amer. Chem. Soc.* **95**, 3770 (1973).

substituted uracils,^{356,540} and cytosine.⁵³⁹ The observed resonances for all the nucleosides clearly separate into those due to the sugar carbons and those due to the carbon atoms of the pyrimidine bases. The shifts of the carbon atoms for cytosine, uracil, thymine, 5-halouracils, as well as for some selected pyrimidine nucleosides are collected in Table XXXVII.

The similarity in the pyrimidine carbon resonances in cytidine and deoxycytidine is indicative of the independence of these shifts from the sugar fragments. The differences observed between the chemical shifts of uracil and thymine, or uridine and thymidine, indicate that they must result from the presence of the 5-methyl group in the latter. The downfield shifts (~ -7.5 ppm) of the C-5 peaks of uracil or uridine upon 5-methyl substitution are typical for a carbon directly substituted by a

TABLE XXXVII

CARBON-13 CHEMICAL SHIFTS^a IN THE PYRIMIDINE RING OF URACIL, THYMINE, 5-HALOURACILS AND SELECTED PYRIMIDINE NUCLEOSIDES

Compound ^b	Carbon positions			
	C-2	C-4	C-5	C-6
Uracil	-24.24	-36.70	+27.60	-14.48
Thymine	-23.69	-37.10	+20.10	-9.90
5-F-uracil	-22.34	-30.17	-12.09	+1.43
5-Cl-uracil	-22.86	-32.19	+21.86	-11.95
5-Br-uracil	-23.06	-32.33	+33.40	-14.41
5-I-uracil	-23.54	-33.78	+60.24	-19.27
Uridine	-23.88	-36.20	+25.46	-13.68
4-Thiouridine	-20.59	-62.57	+14.83	-8.39
2,4-Dithiouridine	-45.26	-58.47	+9.84	-7.02
Thymidine	-23.06	-36.27	+18.02	-8.80
4-Thiothymidine	-20.20	-62.99	+9.71	-5.66
Cytosine ^c	-38.4	-42.5	+34.6	-29.6
Cytidine ^c	-28.0	-38.0	+33.1	-14.4
Cytidine	-28.42	-38.17	+32.85	-14.29
Deoxycytidine	-28.49	-38.44	+32.67	-13.93
2-Thiocytidine	-52.36	-32.56	+29.54	-14.15

^a Shifts given in parts per million relative to benzene. Positive values indicate higher field. Data for uracil and thymine taken from Tarpley and Goldstein³⁵⁶ and those for nucleosides from Jones *et al.*⁸⁰ (see footnote c).

^b Cf. ref. 540 for the ¹³C chemical shifts in 5-substituted uracils.

^c Data taken from Schweizer *et al.*⁵³⁹ Shifts were measured from external hexafluorobenzene and converted to a benzene scale.

⁵⁴⁰ P. D. Ellis, R. B. Dunlap, A. L. Pollard, K. Seidman, and A. D. Cardin, *J. Amer. Chem. Soc.* **95**, 4398 (1973).

methyl group. Substitution of carbonyl oxygen by sulfur at C-4 in uridine provides a significant downfield shift (-26.4 ppm), the C-4 line being the lowest field line in the pyrimidine group. Similar significant downfield shifts (-21.4 to -26.7 ppm) are observed for the carbon atoms at which the carbonyl oxygen is replaced by sulfur. In all the compounds listed in Table XXXVII the chemical shifts were found in the order C-4 > C-3 > C-6 > C-5.

Several groups of workers have attempted to relate the ^{13}C chemical shifts to the π -electron densities or total charge densities in aromatic systems as well as in nitrogen containing heterocycles. For the pyrimidine bases, Jones *et al.*^{79,80} have plotted the observed ^{13}C chemical shifts against the π -electron densities calculated by means of the π -HMO π -SCF MO, or *ab initio* methods as well as against the total gross population derived from nonempirical calculations. A similar comparison is shown in Fig. 21. Although the $\delta_{13\text{c}}$ values relate better to the π -charges than to the total ones, it seems from Fig. 21 that a simple correlation of π -charge with ^{13}C chemical shift is inadequate.^{540a} This is not unexpected, as Karplus and Pople⁵⁴¹ have shown that the ^{13}C chemical shifts depend on a variety of additional contributing factors (variations in the π -electron densities and mobile bond orders, the effect of σ -bond polarization in the C-H bond).

Tarpley and Goldstein³⁵⁶ have correlated the ^{13}C chemical shifts in uracil, thymine, and 5-halouracils with the π - or total charge densities calculated with EHT method. The $\delta_{13\text{c}}$ values correlate quite well with the charges if the individual carbon positions are considered separately.

The $\delta_{13\text{c}}$ values for the 5-halouracils correlate also quite well with the electronegativity of the halogens. Linear correlations have been obtained between the directly bonded ^{13}C -H couplings and the substituent electronegativity parameters of Dailey and Schoolery⁵⁴² for 5-halouracils. However, recently Ellis *et al.*⁵⁴⁰ studying the ^{13}C chemical shifts in 17 5-substituted uracils, showed that there was no obvious relationship between $\delta_{13\text{c}}$ of C-5 and C-6 in uracils and the electronegativities of the substituents. On the other hand, they found a close

^{540a} Comparing the ^{13}C chemical shifts in uracil, thymine, cytosine with those in the corresponding nucleosides it can be seen that the addition of the sugar to the base causes an upfield shift of the four peaks of the bases, and that the shifts of the C-2 and C-6 peaks in cytosine ($+10.4$ and $+15.2$ ppm, respectively) are exceptionally great. In general, however, the relationships between the $\delta_{13\text{c}}$ values and $\Delta q_{\text{ENDO/2}}$ are not significantly changed when the $\delta_{13\text{c}}$ values for cytosine are used instead of those for cytidine.

⁵⁴¹ M. Karplus and J. A. Pople, *J. Chem. Phys.* **38**, 2803 (1963).

⁵⁴² B. P. Dailey and J. N. Schoolery, *J. Amer. Chem. Soc.* **77**, 3977 (1955).

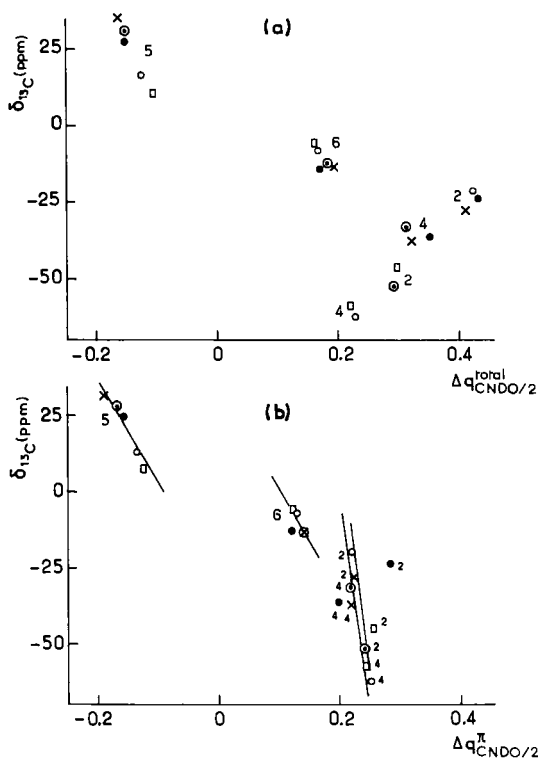


FIG. 21. Observed ^{13}C chemical shifts, $\delta_{13\text{C}}$, for uridine (●), 4-thiouridine (○), 2,4-dithiouridine (□), cytidine (×), and 2-thiocytidine (⊙) plotted against the net total charges (a) or net π -charges (b) calculated by CNDO/2 method for the corresponding bases.

linear relationship between the $\delta_{13\text{C}}$ of C-5 in the uracils and those for the carbons bearing the substituent in a series of monosubstituted benzenes.

The ^{15}N magnetic resonance studies of the pyrimidine bases or their derivatives are scarce. Roberts *et al.*⁸⁵ have measured the ^1H and ^{15}N magnetic resonance spectra of a number of pyrimidines including uracil and 1-methylcytosine. The most important result of this study was the elucidation of the dominant tautomeric structures of uracil and protonated 1-methylcytosine as the diketo, **32**, and keto-amine form, **7**, respectively (cf. Sections II and IV and the spectrum of 1-methylcytosine hydrochloride labeled only in the amino group⁶²). In the case of uracil,⁸⁵ the two ^{15}N -bonded protons gave two doublets centered at 10.78 and 10.96 ppm (measured downfield from internal tetramethyl-

silane), each of which was perturbed by further couplings. The lowfield doublet was assigned to ^{15}N -3.

The ^{15}N chemical shifts as well as the coupling constants $J_{\text{H},15\text{N}}$ in the bases, and related compounds have not been interpreted theoretically. On the other hand, the magnitude of the coupling constants has been predicted from the molecular structure with reasonable accuracy by means of CNDO/2 calculations for pyrimidine, pyridine, or pyrazole.⁵⁴³ We can expect that a similar prediction of the spin-spin coupling constants may be made for the pyrimidine and purine nucleic acid bases.

Very recently, the pure *nuclear quadrupole resonance* (NQR) of ^{14}N has been observed in pyrimidine and purine nucleic acid bases, their nucleosides, and some related model compounds^{91,92} using the double nuclear resonance method.⁵⁴⁴⁻⁵⁴⁶ Observed NQR transition frequencies provide the quadrupole coupling constants and electric field gradient asymmetry parameters. The field gradient and the corresponding asymmetry parameter η are a sensitive measure of the electronic charge distributions in the vicinity of the nucleus. However, the field gradient is not measurable itself, and usually both quantities are calculated. Unfortunately, to date even all electron *ab initio* calculations of quadrupole resonance data on such molecules as pyrrole, pyridine, and related types do not yield very satisfactory results.⁵⁴⁷ In the case of the pyrimidine bases, the nuclear quadrupole coupling constants have been interpreted in terms of semiempirical approximations. The constants have been compared⁹¹ to π -orbital population on corresponding nitrogens of the bases. A definite correlation was observed between the experimental data and the theoretical indications.

⁵⁴³ J. P. Jacobson, O. Snerling, E. J. Pederson, J. T. Nielsen, and K. Schaumberg, *J. Magn. Reson.* **10**, 130 (1973).

⁵⁴⁴ S. R. Hartmann and E. L. Hahn, *Phys. Rev.* **128**, 2042 (1962).

⁵⁴⁵ F. M. Lurie and C. P. Slichter, *Phys. Rev.* **133**, A1108 (1964).

⁵⁴⁶ R. E. Slusher and E. L. Hahn, *Phys. Rev.* **166**, 332 (1968).

⁵⁴⁷ E. Kochanski, J. M. Lehn, and B. Levy, *Chem. Phys. Lett.* **4**, 75 (1969).

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Recent Advances in the Chemistry of Benzo[b]furan and Its Derivatives. Part I: Occurrence and Synthesis

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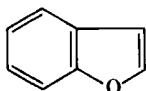
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I. Introduction

Since it was first synthesized by Perkin in 1870 and discovered in coal tar by Kraemer and Spilker in 1890, benzo[b]furan (1) has been the subject of much research. Several important monographs have been devoted to it,¹⁻³ and many publications including a chapter on benzo[b]furan have appeared recently; they will be mentioned in the course of this survey of the chemistry of benzo[b]furan and of its main derivatives, which covers the period 1951-1972. The Appendix contains additional references to January 1974.

The importance of the benzo[b]furan ring system in natural substances and in synthetic products with pharmacodynamic applications explains the large number of papers published. Our aim is not to make an exhaustive study, but rather to underline the important aspects of the modern chemistry of benzo[b]furan and its derivatives:



(1)

The present chapter represents the first part of this study and is devoted to the natural occurrence and to the general methods of synthesis of benzofuran and its derivatives. Structural and spectrographic properties as well as the chemical reactivity of these compounds will be covered in a later chapter.

A. NOMENCLATURE

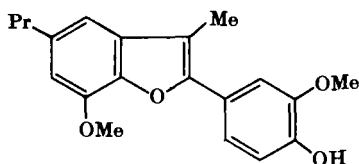
The accepted name for 1 in *Chemical Abstracts* is benzo[b]furan. To shorten complicated names, we shall systematically drop the [b] in the course of this survey, since all the compounds discussed are derived

¹ R. Dolique, in "Traité de Chimie Organique," Vol. 18, pp. 222-259. Masson, Paris, 1945.

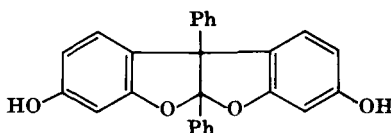
² V. B. Meyer, in "Heterocyclic Compounds" (H. C. Elderfield, ed.), Vol. 2, pp. 1-65. Wiley, New York, 1951.

³ T. S. Stevens, in "Chemistry of Carbon Compounds" (E. M. Rodd, ed.), Vol. IV_A, pp. 168-185. Elsevier, Amsterdam, 1957.

from this one structure. We believe that the name coumarone, frequently used for simple benzofurans, should be rejected, as also the names coumaran for 2,3-dihydrobenzofuran and coumaranone for 3(2*H*)-benzofuranone. On the other hand, we shall utilize the name coumarin for benzopyran-2-one, which is to be found in *Chemical Abstracts*, although, with such similar names, printing mistakes may give rise to confusions that obscure the reading of some papers. Many such mistakes have been found in the literature: for instance, compound **2** is named "3-methyl-5-propyl-7-methoxy-2-(4-hydroxy-3-methoxyphenyl)couma-



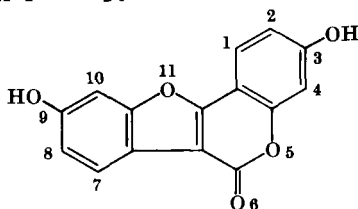
(2)



(3)

ran,"⁴ whereas the formula shown is that of a benzofuran. Similarly, the condensation product of benzil with resorcinol,⁵ named "3,8-dihydroxy-5a,10b-diphenylcoumarano[2',3':2,3]coumarin" (as in *Chemical Abstracts*⁵), or "3,8-dihydroxy-5a,10b-diphenylcoumarano[2',3':2,3]-coumaran (3) (original text) is in fact 5a,10b-dihydro-3,8-dihydroxy-5a,10b-diphenylbenzofuro[2,3-*b*]benzofuran (*Chemical Abstracts*, Subject Index **69**, 427). 3-Bromocoumarone (3-bromobenzofuran) appears as 3-bromocoumarin.⁶ And so on.

In complex heterocyclic compounds, the terms coumarano, coumarono, coumarino are therefore rejected, although they allow a shortening of the occasionally somewhat cumbersome and forbidding *Chemical Abstracts* nomenclature: thus, coumestrol (**4**) will not be called the dihydroxy derivative of coumarono[3,2-*c*]coumarin,⁷ but 3,9-dihydroxy-6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one.



(4)

⁴ A. Spetz, *Acta Chem. Scand.* **8**, 360 (1954).

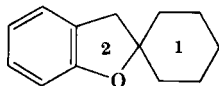
⁵ A. Bunn, M. E. A. Cudby, and J. C. McGowan, *Rec. Trav. Chim.* **87**, 599 (1968); *Chem. Abstr.* **69**, 43822 (1968).

⁶ M. Martynoff, *C. R. Acad. Sci.* **233**, 878 (1951); *Chem. Abstr.* **47**, 8725 (1953).

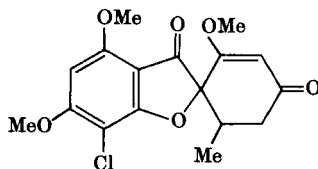
⁷ J. Dupayrat, "Structure et Nomenclature des Hétérocycles," p. 121. Technip, Paris, 1970.

Simpler names for compounds of type 4 (mentioned in the guiding index of *Chemical Abstracts*) will be used in this survey: the fundamental heterocycle 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one is called coumestan.⁸ Coumestrol (4) becomes 3,9-dihydroxycoumestan. Another derivative of the same family, waedelolactone,⁹ is 3-methoxy-1,8,9-trihydroxycoumestan. In this connection, it would be advisable, for natural compounds of botanical origin, to put the corresponding chemical name in brackets.

Another simplified nomenclature adopted here relates to natural spiro-2,3-dihydrobenzofuran derivatives, such as griseofulvin. The fundamental heterocycle, named grisan, being spirobenzofuran-2(3*H*)-1'-cyclohexane (5), griseofulvin (7-chloro-4,6,2'-trimethoxy-6'-methylspirobenzofuran-2(3*H*)-1'-[2]cyclohexene-3,4'-dione) (6) becomes 7-chloro-4,6,2'-trimethoxy-6'-methyl-2'-grisene-3,4'-dione.

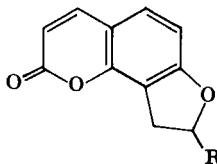
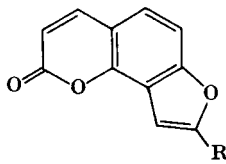


(5)



(6)

In the field of furocoumarins, which includes a large number of compounds extracted from the Umbelliferae, the nomenclature is rather uncertain. Up to 1968, those compounds were looked upon (*Chemical Abstracts*) as δ -lactones of Bz-*o*-hydroxybenzofurylacrylic acids; more recently, as furochromenic derivatives.¹⁰ Some of those compounds have names related to their geographical or botanical origin, such as sachalinin (7), recently extracted from the roots of *Angelica sachalinensis*;¹¹ it is then advisable to add the chemical name.

(7) R = $-\text{C}(\text{CH}_2\text{OH})=\text{CH}_2$ (8) R = $-\text{CMe}=\text{CH}_2$ (9) R = $-\text{CMe}_2\text{OH}$

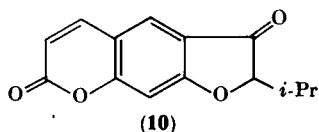
⁸ C. Deschamps-Vallet and C. Mentzer, *C. R. Acad. Sci.* **251**, 736 (1960).

⁹ T. R. Govindachari, L. Nagarajan, B. R. Pai, and P. C. Parthasarathy, *J. Chem. Soc.*, 545 (1957).

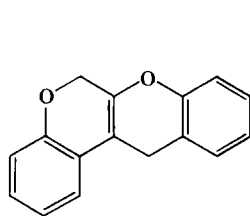
¹⁰ R. Royer, P. Demerseman, J. F. Rossignol, and A. Cheutin, *Bull. Soc. Chim. Fr.*, 2072 (1971).

¹¹ G. K. Nikonov, *Khim. Prir. Soedin.* **6**, 623 (1970); *Chem. Abstr.* **74**, 76262 (1971).

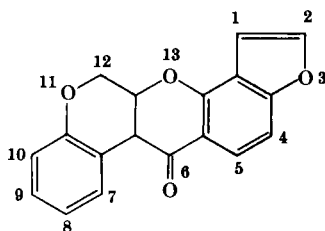
Other furocoumarins, although they have rather different structures, have very similar names, which gives rise to confusion. Thus, whereas oroselone (8) is 8-isopropenyl-2*H*-furo[2,3-*h*][1]benzopyran-2-one¹² and oroselol (9) is 8-(1-hydroxy-1-methylethyl)-2*H*-furo[2,3-*h*][1]benzopyran-2-one, oreoselone (10) is 2-isopropyl-2,3-dihydro-7*H*-furo[3,2-*g*][1]benzopyran-3,7-2*H*-dione.¹³



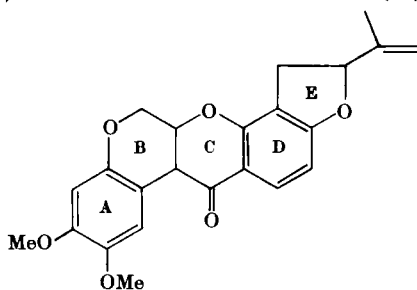
Several systems of nomenclature have been used for rotenoids, some of which have been synthesized from dihydrobenzofuran derivatives.



(11)



(12)



(13)

Thus, according to Dupayrat,⁷ the basic heterocycle is chromeno-[3,4-*b*]chromene (11). Consequently, rotenoids are furo[2,3-*h*]chromano-[3,4-*b*]chromanones (12), and rotenone (13) is 2-isopropenyl-8,9-dimethoxy-6-oxo-1,2,6a,12a-tetrahydrofuro[2,3-*h*]chromeno[3,4-*b*]chromene. On the other hand, compound 11 has been given a global name, rotoxene,^{14,15} which makes the nomenclature more manageable, but does not seem to have been generally accepted. The nomenclature here adopted for rotenoids is that of *Chemical Abstracts*; unfortunately this has

¹² B. E. Nielsen and S. Lemmich, *Acta Chem. Scand.* **18**, 932 (1964).

¹³ O. Dann and G. Volz, *Justus Liebigs Ann. Chem.* **631**, 102 and 111 (1960).

¹⁴ J. Ringshaw and H. J. Smith, *Chem. Ind. (London)*, 1383 (1965).

¹⁵ J. R. Ringshaw and H. J. Smith, *J. Chem. Soc. C*, 102 (1968).

varied somewhat: in 1958, we find for **13** "8,9-dimethoxy-2-isopropenyl-1,2,12,12a-tetrahydrobenzofuro [4,5-*b*] [1] benzopyrano [4,3-*e*] pyran-6 [6aH] one"; in 1970, this becomes "8,9-dimethoxy-2-isopropenyl-1,2,12,12a-tetrahydro [1] benzopyrano [3,4-*b*] furo [2,3-*h*] benzopyran-6 [6aH] one."

It is highly desirable that a coherent and final nomenclature¹⁶ be adopted on the international level. Finally it seems to us that the use of two names for the same compound such as coumarone and benzofuran, in the same paper,¹⁷ is undesirable.

B. GENERALITIES ON BENZOFURAN DERIVATIVES

Since the end of World War II, the chemistry of benzofuran derivatives has developed in a spectacular fashion: research in this field has reached such a scale that the period covered by this review has given rise to a larger number of papers than that between 1870 and 1950. It has proceeded along the following three main lines:

1. Extraction, determination of structures, partial or total synthesis of the simple or complex heterocyclic derivatives constituting the natural benzofuran derivatives of vegetable origin.

2. Synthesis of benzofuran derivatives with physiological, pharmacological, therapeutic, or toxic properties.

3. Studies on the reactivity of benzofuran and its derivatives from the chemical and physical point of view (determination of constants, calculation of orbitals, spectrographic data). In most of the recent papers, structural determination and reaction mechanism interpretation has increasingly relied upon spectroscopic methods. This has produced a considerable amount of data, which cannot fully be covered within the scope of this survey.

As regards *natural* substances, we shall survey only those syntheses starting from nonfused benzofuran derivatives: *furocoumarins*¹⁸ (lactones of Bz-*o*-hydroxybenzofurylacrylic acids); *furochromones*¹⁹ (from *o*-hydroxylated Bz-benzofuranic β -diketones); *furoquinolines*²⁰ (from Bz-aminobenzofurans).

¹⁶ We shall use the rules of the IUPAC Nomenclature of Organic Chemistry, Butterworth, London 1971.

¹⁷ V. J. André, J. Dath, J. Mahieu, and E. H. Grand'ry, *Brennst. Chem.* **48**, 369 (1967).

¹⁸ B. E. Nielsen, "Coumarins of Umbelliferous Plants," p. 199. Roy. Danish School Pharmacy, Copenhagen, 1970.

¹⁹ Ch. P. Hutterer and E. Dale, *Chem. Rev.* **48**, 543 (1951).

²⁰ H. T. Openshaw, in "The Alkaloids" (R. H. F. Manske, ed.), Vol. VII, pp. 233-241. Academic Press, New York, 1960.

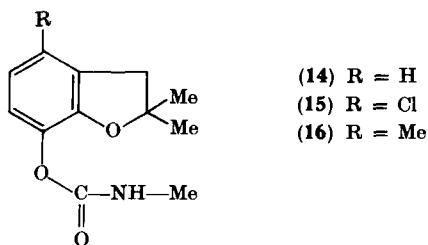
Coumestans,²¹ although they have a fused benzofuran ring, will be surveyed as being δ -lactones of 2-(2-hydroxyphenyl)-3-benzofuran carboxylic acids [coumestrol (4)²² is the δ -lactone of 2-(2,4-dihydroxyphenyl)-6-hydroxy-3-benzofurancarboxylic acid]. The synthesis of some rotenoids²³ from benzofuran derivatives will also be reviewed, but dibenzofuran derivatives, such as usnic acid and its derivatives, will not be treated.

Many substances with physiological, pharmacological, therapeutic, or toxic properties are to be found among natural products with a benzofuran ring. As to *synthetic* benzofuran derivatives prepared for the study of their physiological properties, their number is large. However, only a few are active (one therapeutically active out of 3500 synthesized on the average).^{24,25} Nevertheless, their numbers are much larger than in the benzothiophene series.

C. PHYSIOLOGICAL PROPERTIES

1. Toxic or Insecticidal Simple and Complex Benzofurans

Pesticidal carbamates with 2,3-dihydrobenzofuran structures: carbofuran or NIA-9242 is methyl 2,3-dihydro-2,2-dimethyl-7-benzofuranyl-carbamate (14); NIA 10559 (15) is its 4-chloro, and NIA 10586 (16) its 4-methyl derivative. Benzofuran itself, 2,3-dibromobenzofuran and 2,3-dihydro-3-oxobenzofuran and their derivatives have very low or zero activity.²⁶



“Euparinoid” *natural benzofurans* such as tremetol, a mixture of several compounds (see Section III), the main one being tremetone (17),

²¹ E. Wong, *Fortschr. Chem. Org. Naturstoffe* **28**, 1 (1970).

²² E. M. Bickloff, R. R. Spencer, S. C. Witt, and B. E. Knucles, *U.S. Dept. Agr. Tech. Bull.* **1408** (1969); *Chem. Abstr.* **72**, 117545 (1970).

²³ L. Crombie, *Fortschr. Chem. Org. Naturstoffe* **21**, 275 (1963).

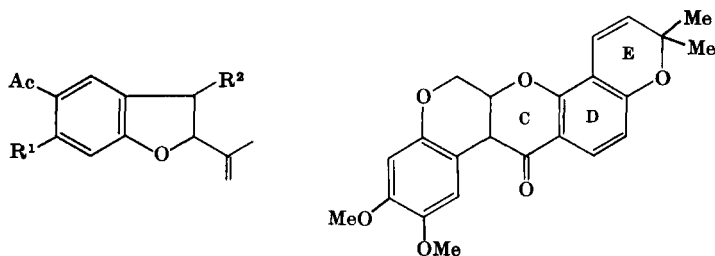
²⁴ J. P. Garnier, “Actualités de Chimie Thérapeutique,” p. 9. *Edifor, Paris*, 1971.

²⁵ P. N. Craig, H. C. Caldwell, W. G. Groves, *J. Med. Chem.* **13**, 1079 (1970).

²⁶ V. Prey, F. Beran, and H. Böhm, *Mitt. Chem. Forschungsinst. Wirt. Oesterr.* **6**, 28 (1952); *Chem. Abstr.* **46**, 8802 (1952).

are ichthyotoxic^{27,28} and responsible for ailments such as "trembles" in cattle and "milk sickness" in human beings (a serious and incurable condition). The toxic compound responsible for those illnesses seems to be a minor component of tremetol: toxol (18) or 5-acetyl-2,3-dihydro-3-hydroxy-2-isopropenylbenzofuran. The bacteriostatic action of this compound has been investigated.²⁹

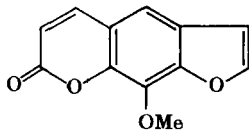
Tremetone (17) seems also to have insecticidal properties^{27,30a,b} similar to those of rotenone (13)³¹ (and half its ichthyotoxic action). It should be noticed that the structure of tremetone is similar to rings C, D, and E of rotenone.



(17) $R^1 = R^2 = H$

(18) $R^1 = H$ $R^2 = OH$

(19)



(20)

Deguelin (19),³² in which rings D and E have a chromene, not a benzofuran, structure, is fully as ichthyotoxic and insecticidal as rotenone. It has been suggested³³ that the "toxophore" in rotenoids might be the sequence $=CH-CH=CH-O-$ in rings C and D, which is found both in (13) and in (19). The same sequence is found in

²⁷ D. M. Bowen, J. I. De Graw, J. R. Shah, and W. A. Bonner, *J. Med. Pharm. Chem.* **6**, 315 (1963).

²⁸ S. O. Butler, "Fractions of Tremetol and Their Toxicities," M.Sc. Thesis, Oklahoma Agr. Mech. College, Stillwater, Oklahoma, 1945.

²⁹ L. H. Zalkow, N. Burke, G. Cabat, and E. G. Grula, *J. Med. Pharm. Chem.* **5**, 1342, 2222 (1962).

^{30a} F. Binon, *Conf. Pleniére, Rencontres Chim. Ther.*, 7emes, 1971.

^{30b} F. Binon, *Chim. Ther.* **7**, 156 (1972).

³¹ L. Feinstein and M. Jacobson, *Fortsch. Chem. Org. Naturst.* **10**, 463 (1963).

³² M. Miyano, T. Nishikubo, and M. Matsui, *Chem. Ber.* **93**, 1746 (1960).

³³ L. Ramachandran Row and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A* **34**, 187 (1951).

euparinoids, such as euparin (6-hydroxydehydrotremetone) and 6-hydroxytremetone, the physiological properties of which are little known as yet.³⁴

Furocoumarins, such as xanthotoxin (**20**), are also strongly ichthyotoxic.³⁵ It is not yet possible to deduce the toxophore responsible for these physiological properties.

2. Antihelmintic, Parasiticial, and Nematocidal Benzofuran Derivatives

In the group of synthetic benzofurans are found nitro derivatives with the nitro group on the benzofuran ring.³⁶⁻³⁸ It is difficult to attribute these properties to a definite "toxophore," isopropyl derivatives being at least as active as nitro derivatives. Nitrobenzofurans are also bactericidal.^{39,40} A parallel between structure and antibacterial activity has been made in the nitrofuran series.⁴¹

2,3-Dihydro-2-hydroxy-6-methyl-3-methylenebenzofuran,^{42,43} a simple natural benzofuran, has nematocidal properties.

3. Bactericidal, Antifungal, and Antibiotic Benzofuran Derivatives

Natural griseofulvin and its synthetic derivatives,⁴⁴ as well as natural and synthetic furoquinolines,⁴⁵ show such properties, as do some pterocarpans, such as phaseolidin,⁴⁶ which is antifungal and lipophilic (**21**).

³⁴ T. Cheng, Ph. D. Thesis, Utah Univ. 1964.

³⁵ M. E. Brökke and B. E. Christensen, *J. Org. Chem.* **23**, 589 (1958).

³⁶ Y. Kawase, R. Royer, M. Hubert-Habart, A. Cheutin, L. René, and J. P. Buisson, *Bull. Soc. Chim. Fr.*, 3131 (1964).

³⁷ R. Cavier, R. Royer, R. Rips, and L. René, *Chim. Ther.* **4**, 21 (1969).

³⁸ R. Royer, *Chim. Ther.* **4**, 389 (1969).

³⁹ L. J. Powers and M. P. Mertes, *J. Med. Chem.* **13**, 1102 (1970).

⁴⁰ A. Annaji Rao, and N. V. Subba Rao, *Symp. Syn. Heterocycl. Comp., Physiol. Interest. Proc.* **96**, 30 (1966); *Chem. Abstr.* **69**, 18955 (1968).

⁴¹ K. Hirano, S. Yoshina, K. Okamura, and I. Suzuki, *Bull. Chem. Soc. Jap.* **40**, 2224 (1967).

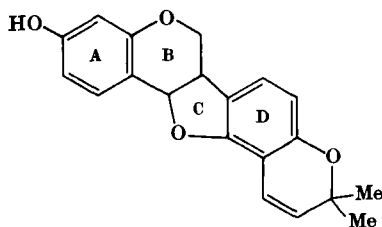
⁴² F. J. Gommers, *Phytochemistry* **10**, 1945 (1971).

⁴³ F. Bohlmann, J. Schutz, and U. Bohlmann, *Tetrahedron Lett.*, 4703 (1969).

⁴⁴ F. J. Grove, *Fortsch. Chem. Org. Naturst.* **22**, 203 (1964).

⁴⁵ R. Royer and P. Demerseman, *Ind. Chim. Belge* **32**, 286 (1967); *Chem. Abstr.* **70**, 77671 (1969).

⁴⁶ D. R. Perrin and C. P. Whittle, *Tetrahedron Lett.*, 1673 (1971).

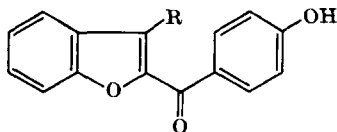


(21)

Menthofuran (3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran),^{47,48} 2-ethyl-3-benzofurylpenicillin,⁴⁹ and the α -(benzofuryloxy)acetyl derivative of 7-aminocephalosporanic acid,⁵⁰ are also bactericidal.

4. Estrogenic Benzofurans

a. *Synthetic Benzofurans.* 2-(4-Hydroxybenzoyl)benzofuran (22a) and its 3-ethyl derivative (22b) are estrogenic.^{51,52} Many derivatives in this class have been synthesized, but they do not seem to have better estrogenic properties than 22a.



(22a) R = H

(22b) R = Et

b. *Natural Benzofurans.* Coumestrol (4)⁵³⁻⁵⁷ is, together with

⁴⁷ H. G. Daessler, *Pharmazie (Weinheim)* **12**, 87 (1957).

⁴⁸ H. G. Daessler and G. Hube, *Anz. Schaedlingskunde* **30**, 86 (1957).

⁴⁹ F. P. Doyle and J. A. C. Naylor, U.S. Patent 3, 470, 151 (1969); *Chem. Abstr.* **72**, 21682 (1970).

⁵⁰ K. Hattori and J. Hirai, Japanese Patent 6, 925, 789 (1969); *Chem. Abstr.* **72**, 12747 (1970).

⁵¹ N. P. Buu-Hoi, in "Les Hétérocycles Oxygénés," Colloq. Int. CNRS, p. 121. CNRS, Paris, 1957.

⁵² E. Bisagni, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 3693 (1955).

⁵³ E. M. Bickoff, A. N. Booth, E. L. Lyman, A. L. Livingston, C. R. Thompson, and C. O. Kohler, *J. Agr. Food. Chem.* **6**, 536 (1958).

⁵⁴ W. D. Kitts, E. Swestra, W. C. Brink, and A. J. Wood, *Can. J. Animal Sci.* **39**, 158 (1959).

⁵⁵ E. M. Bickoff and A. N. Booth, U.S. Patent 2, 929, 713 (1960); *Chem. Abstr.* **54**, 13147 (1960).

⁵⁶ E. M. Bickoff, A. L. Livingston, and A. N. Booth, U.S. Patent 3,077,404 (1963); *Chem. Abstr.* **59**, 1592 (1963).

genistein (an isoflavonoid), one of the phytoestrogenic substances (non-steroid estrogens) that stimulate animal growth. Methylation of the hydroxyl groups considerably reduces the estrogenic activity (by 75% in the case of 3,9-di-*O*-methylcoumestrol⁵⁷). The estrogenic activity of coumestrol is used in ways similar to those of stilbestrol.^{58,59}

Phytoestrogens seem to alter the sexual development of animals by acting on the hypothalamic system of hypophyseal regulation⁶⁰ (in spite of the results of other authors⁶¹).

5. Benzofurans with Antispasmodic and Vasodilating Activity

a. *Synthetic Benzofurans.* 2-(4-Hydroxybenzyl)benzofuran has a relaxing effect "on the histamine and acetylcholine spasm and the motility of guinea pig intestine more pronounced than that of khellin itself," but estrogenic activity precludes its clinical use.⁶² Among many 3-alkyl-2-arylbenzofurans and 2-alkyl-3-arylbenzofurans synthesized,^{62,63} therapeutically effective compounds are: 2-ethyl-3-(4-hydroxybenzoyl)benzofuran (**23a**), or Benzarone,⁶⁴ angiotropic, antiinflammatory, and fibronolytic (used clinically under the name Fragivix L); 2-ethyl-3-(3,5-diiodo-4-hydroxybenzoyl)benzofuran (**23b**), or benziodarone (clinically used as Amplivix,⁶⁵ a coronary vasodilator).

The corresponding 3,5-dibromo derivative is benzbromarone, which is less active. The last two compounds are, besides, powerful uricoc-eliminators;^{60a} 2-ethyl-3-(3,4,5-trimethoxybenzoyl)benzofuran (**23c**)⁶⁶ and 2-butyl-3-[3,5-diiodo-4-(2-diethylaminoethoxy)benzoyl]benzofuran or amiodarone (**24**) (or Cordarone⁶⁷) are powerful angiotropics.

⁵⁷ E. M. Bickoff, R. L. Lyman, A. L. Livingston, and A. N. Booth, *J. Amer. Chem. Soc.* **80**, 3969 (1958).

⁵⁸ L. Jurd, U.S. Patent 3,165,537 (1963); *Chem. Abstr.* **62**, 7728 (1965).

⁵⁹ L. Jurd, *J. Org. Chem.* **24**, 1786 (1959).

⁶⁰ W. W. Leavitt and D. M. Meisner, *Nature (London)* **218**, 181 (1968).

⁶¹ B. Maymone, *Ann. Inst. Sper. Zootech.* **10**, 195-225 (1963); *Chem. Abstr.* **66**, 72878 (1967).

⁶² N. P. Buu-Hoï, E. Bisagni, R. Royer, and C. Routier, *J. Chem. Soc.*, 625 (1957).

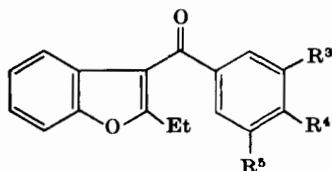
⁶³ Société des Laboratoires Labaz, Belgian Patent 553,621 (1957); *Chem. Abstr.* **53**, 22016 (1959).

⁶⁴ F. Chaillet, G. Barchewitz, R. Charlier, A. Guibert, M. Colot, and G. Deltour, *Arzneim.-Forsch.* **20**, 358 (1970).

⁶⁵ M. Mazière, N. P. Buu-Hoï, and N. Dat Xuong, *Bull. Soc. Chim. Fr.*, 1000 (1963).

⁶⁶ M. Yokoyama, S. Kawano, and Y. Mori, Japanese Patent 64/10,344; *Chem. Abstr.* **61**, 11972 (1964).

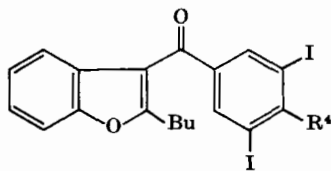
⁶⁷ R. Charlier, G. Deltour, A. Baudine, and F. Chaillet, *Arzneim.-Forsch.* **18**, 1408, (1968).



(23a) $R^4 = OH$ $R^3 = R^5 = H$

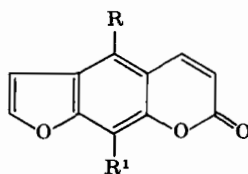
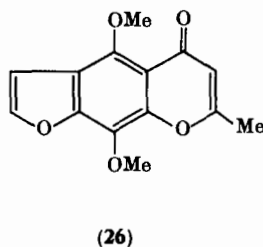
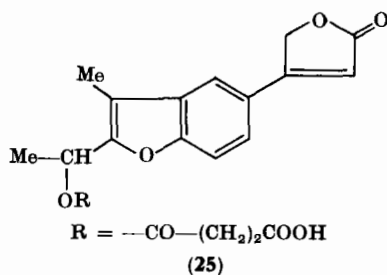
(23b) $R^3 = R^5 = I$ $R^4 = OH$

(23c) $R^3 = R^4 = R^5 = OMe$



(24) $R^4 = O-CH_2-CH_2-N \begin{matrix} Et \\ Et \end{matrix}$

In the 3-phenyl-2(3*H*)-benzofuranone series, we find a long-known spasmolytic compound, 3-(2-diethylamino)ethyl-3-phenyl-2(3*H*)-benzofuranone^{30a,68a,b} (Amolanone), which also has analgesic properties. A novel compound, 2-(1-succinyloxy)ethyl-3-methyl-5-(2-oxo-2,5-dihydro-4-furyl)benzofuran or Benfurodil⁶⁹ (25) (clinical name Eudilat), is a vasodilator and cardiotonic.



(27a) $R = R^1 = H$

(27b) $R = OMe$ $R^1 = H$

(27c) $R = H$ $R^1 = OMe$

b. *Natural Benzofurans.* Furochromones, such as khellin (26), are spasmolytics, effective against bronchial asthma;^{70,71} their electronic

^{68a} Abbot Lab., British Patent 627,834, (1949); *Chem. Abstr.* **44**, 3530 (1950).

^{68b} A. W. Weston and M. A. Spielman, U.S. Patent 2,513,698 (1950); *Chem. Abstr.* **44**, 8956 (1950).

⁶⁹ J. Schmitt, M. Suquet, J. Salle, P. Comoy, G. Callet, and J. Le Meur, *Chim. Ther.*, 305 (1966).

⁷⁰ A. Burger, "Medicinal Chemistry," Vol. I, p. 238. (Wiley Interscience), New York, 1951.

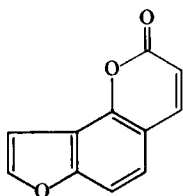
⁷¹ R. Charlier, "Coronary Vasodilators." Pergamon, London, 1961.

structure and polarization have been paralleled in those of 3-acylbenzofurans.³⁸ Some furocoumarins⁷² are also highly spasmolytic (e.g., those in beroxan, a mixture of 4- and 9-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one, **27b** and **27c**).

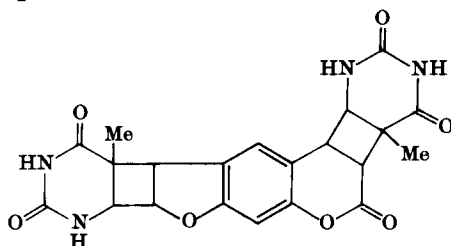
6. Photosensitizing (or Better Phototoxic⁷³) Properties

Only one class of benzofuran derivative, natural or synthetic, shows this property—the *furocoumarins*; these are important for plant biosynthesis, since they take part in the elaboration of chlorophyll.^{30a,b}

Among linear furocoumarins, psoralene (**27a**) is particularly active. Angelicin (**28**), another fundamental furocoumarin heterocycle with an angular structure, has only about 12% of the photosensitizing activity of **27a**.^{74,75} On the other hand, it has antibiotic activity. Furochromones have no photosensitizing properties.



(28)



(29)

Substitution at some positions of psoralene reduce the activity, which decreases as the chain becomes longer (the 3-methyl derivative is not very active).⁷⁶ Some compounds, such as 5,9-dihydroxypsoralene,⁷⁷ are used as radiosensitizing drugs, and trioxasalene (2,5,9-trimethylpsoralene) is used as a radioprotective.^{30a,b}

Study of the photoreaction of psoralene⁷⁸ with nucleic acids (DNA) (UV rays, 365 nm) shows that cycloaddition occurs with thymine,

⁷² I. Nowak, G. Buzas, E. Minker, M. Koltai, and K. Szendrei, *Pharmazie (Weinheim)* **20**, 738 (1965); *Chem. Abstr.* **62**, 9460 (1965).

⁷³ L. D. Scheel, "Biochemistry of Some Foodborne Microbial Toxins," Pap. Symp. No. 09118. New York, 1966. MIT Press, Cambridge, Massachusetts, 1967.

⁷⁴ L. Musato, G. Rodighiero, G. Caporale, and C. Antonello, *Farmaco, Ed. Sci.* **13**, 355 (1958).

⁷⁵ M. A. Pathak and T. B. Fitzpatrick, *J. Invest. Dermatol.* **32**, 509 (1959).

⁷⁶ G. Caporale and F. Baccichetti, *Ann. Chim. (Rome)* **60**, 431 (1970).

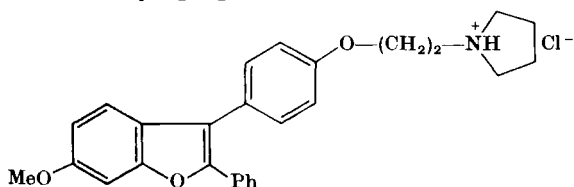
⁷⁷ F. Bordin, L. Bussulini, F. Baccichetti, and R. Bevilacqua, *Ric. Sci.* **39**, 626 (1969); *Chem. Abstr.* **72**, 40788 (1970).

⁷⁸ L. Musajo and G. Rodighiero, *Atti Acad. Naz. Lincei, Cl. Sci. Fis. Nat., Rend.* **50**, 41 (1971).

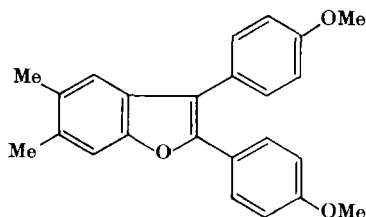
involving one or two molecules of thymine, and giving in the latter case a dicycloaddition compound (29). This may be paralleled in the photoaddition of carcinogenetic hydrocarbons (benzo[a]pyrene⁷⁹) and pyrimidine bases under the same conditions.

Furocoumarins, such as xanthotoxin (20), apparently increase the sensitivity of Ehrlich tumor cells to γ -rays.⁸⁰ The use of phototoxic furocoumarins as anticancer substances has been investigated, but does not seem to give satisfactory results.⁸¹

Some 2,3-diarylbenzofurans, such as 6-methoxy-2-phenyl-3-[*p*-(2-pyrrolidylethoxy)phenyl]benzofuran (hydrochloride) (30), show "anti-fertility" properties in animals.⁸²



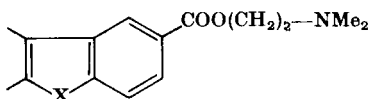
(30)



(31)

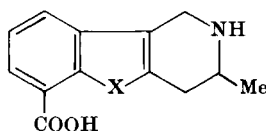
2,3-Bis-(4-methoxyphenyl)-5,6-dimethylbenzofuran (31), has anti-inflammatory activity.⁸³

T-Antiserotonin activity of aminofuran derivatives (32a, 33a) is lower than those of indole derivatives (32b, 33b).⁸⁴



(32a) X = O

(32b) X = NH



(33a) X = O

(33b) X = NH

Many synthetic benzofuran derivatives with an aminoalkyl side chain

⁷⁹ G. M. Blackburn, R. G. Fenwick, and M. H. Thompson, *Tetrahedron Lett.*, 589 (1972).

⁸⁰ F. Bordin, L. Busulini, F. Baccichetti, R. Bevilacqua, and L. Musajo, *Ric. Sci.* **39**, 558 (1969).

⁸¹ G. K. Nikonov and E. M. Vermel, *Puti Sint. Izyskaniya Protivoopukholevykh Prep., Tr. Simp. Khim. Protivoopukholevykh Veshchestv*, 1960, pp. 116-124 (1962); *Chem. Abstr.* **57**, 15247 (1962).

⁸² R. R. Cronshaw, A. T. Jeffries, G. M. Lake, L. C. Chenay, and G. Bialy, *J. Med. Chem.* **14**, 1185 (1971).

⁸³ H. P. S. Chawla, P. K. Grover, N. Anand, V. P. Kamboj, and A. B. Kar, *J. Med. Chem.* **13**, 54 (1970).

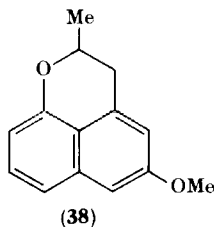
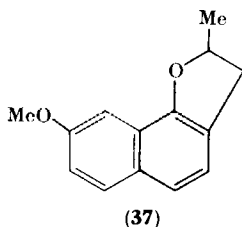
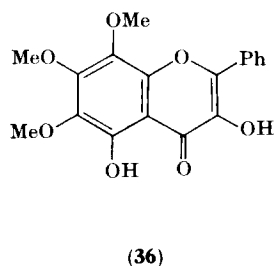
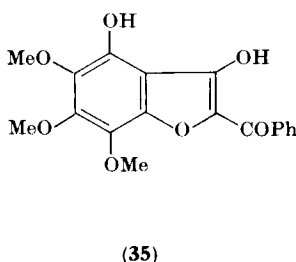
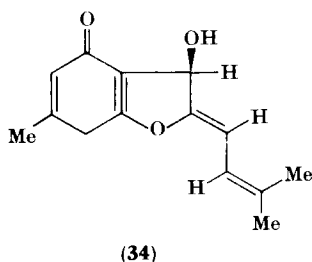
⁸⁴ I. N. Pidevich and N. F. Kucherovala, *Byul. Eksp. Biol. Med.* **72**, 52 (1971); *Chem. Abstr.* **76**, 81209 (1972).

have interesting properties: antitussive,⁸⁵ blocking β -adrenergic,^{86,87} and so on.

Although alkylbenzofuran derivatives (e.g., 2-methyl-2,3-dihydrobenzofuran) have no vitamin F activity,⁸⁸ they seem to show some regulating activity on plant growth.⁸⁹ The 2,2-dimethyl-2,3-dihydrobenzofuran ring is an effective toxophore.⁹⁰

D. CONFIRMATION OF STRUCTURES

Since 1951, the development of modern methods of separation and identification has made it possible to reexamine some structures that were looked upon as established. Here are a few significant examples. Bisabolangelone (34),⁹¹ a sesquiterpenoid hydrobenzofuran alcohol, was initially described as having a furocoumarin structure.⁹² A phenolic compound, once thought to have the structure of an auronol (35),^{93,94}



⁸⁵ M. Descamps and H. Inion, Belgian Patent 704,705 (1968), *Chem. Abstr.* **72**, 78858 (1970).

⁸⁶ R. L. Long and J. Homby, *Biochem. J.* **115**, 668 (1969).

⁸⁷ Imperial Chemical Industries Ltd., Netherlands Appl. 6,500,863 (1965); *Chem. Abstr.* **64**, 3493 (1966).

⁸⁸ P. D. Boyer, M. Robinowitz, and E. Liebe, *J. Biol. Chem.* **192**, 95 (1951).

⁸⁹ C. W. Hargis and H. S. Young, U.S. Patent 3,441,569 (1969); *Chem. Abstr.* **71**, 30355 (1969).

⁹⁰ A. Cruikshank, F. L. Lee, and A. Lupichuk, *J. Med. Chem.* **13**, 1110 (1970).

⁹¹ L. Novotny, S. Samek, and F. Sorm, *Tetrahedron Lett.*, 3541 (1966).

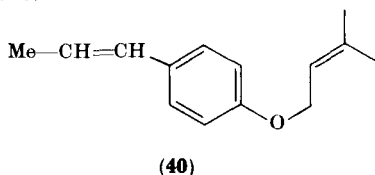
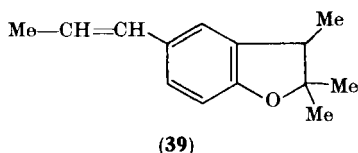
⁹² L. Hörhammer, H. Wagner, and W. Eyrich, *Z. Naturforsch. B* **18**, 639 (1963).

⁹³ J. Vrkoc, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.* **24**, 3938 (1959).

⁹⁴ R. Hansel, H. Rimpler, and R. Schwartz, *Tetrahedron Lett.*, 1545 (1965).

has in fact the isomeric flavonol structure (36) (3,5-dihydroxy-6,7,8-trimethoxyflavone).⁹⁵ Xanthorrhoea resin contains several substances, among which is xanthorrhoein; initially considered to have a naphthofuran structure (37),⁹⁶ the latter is in fact a naphtho[1,8-*bc*]pyran (38).⁹⁷

Reexamination of the extracts of some plants has made it possible to ascertain the presence and the structures of many "minor" compounds.⁹⁸ Anisoxide, isolated from aniseed oil, the structure of which (39) has been established through synthesis,⁹⁹ does not fit in with biogenetic theories and does not show the optical activity normally to be expected from a natural substance: it is actually an artifact, formed during distillation by "abnormal" Claisen rearrangement from compound 40, which is present in the plant.¹⁰⁰



In structural and synthetic chemistry, we also find instances of reconsideration: 3-(3-methoxyphenoxy)-2-butanone gives by ring-closing dehydration a mixture of 2,3-dimethyl-4-methoxybenzofuran and 2,3-dimethyl-6-methoxybenzofuran,¹⁰¹ not just the 6-derivative.¹⁰² 2-Ethyl-7-methoxybenzofuran is not formylated in position 3 by the Vilsmeier-Haack reaction, but in position 4.^{10,103}

E. COMMERCIAL MANUFACTURE

Benzofuran is prepared in semicommercial amounts. Its manufacture from *o*-nitroethylbenzene (as well as that of indole and benzo[*b*]thiophene) has been considered.¹⁰⁴ Alkylbenzofurans are prepared in the pharmaceutical industry as basic products.¹⁰⁵

⁹⁵ R. Hansel, H. Rimpler, and R. Schwartz, *Tetrahedron Lett.*, 735 (1967).

⁹⁶ A. J. Birch and P. Hextall, *Aust. J. Chem.* **8**, 263 (1955).

⁹⁷ A. J. Birch, M. Salahud-Din, and D. C. C. Smith, *Tetrahedron Lett.*, 1623 (1964).

⁹⁸ M. Banda Padhyay, S. B. Malik, and T. R. Seshadri, *Indian J. Chem.* **9**, 731 (1971).

⁹⁹ D. H. R. Barton, A. Bhati, P. De Mayo, and G. A. Morrison, *J. Chem. Soc.*, 4393 (1958).

¹⁰⁰ H. M. Okely and M. F. Grundon, *J. Chem. Soc. D*, 1157 (1971).

¹⁰¹ E. Bisagni and R. Royer, *Bull. Soc. Chim. Fr.*, 925 (1962).

¹⁰² F. H. Curd and A. Robertson, *J. Chem. Soc.*, 714 (1953).

¹⁰³ E. Bisagni, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 3688 (1955).

¹⁰⁴ T. Lesiak, *Chemik* **20**, 404 (1967); *Chem. Abstr.* **69**, 18964 (1968).

¹⁰⁵ A. Areschka, F. Binon, N. Claeys, E. Deray, M. Descamps, C. Goldenberg, F. Henaux, H. Inion, J. M. Maheux, R. Tondeur, and H. J. Ziegler, *Ind. Chim. Belge* **37**, 89 (1972), *Chem. Abstr.* **76**, 153439 (1972).

II. The Presence of Benzofurans in Coal Tar and in Petroleum

A. IN COAL TAR

This question, previously reviewed,^{1,2} still gives rise to a fair amount of research. Benzofuran (**1**) and some of its methylated derivatives (5-methylbenzofuran, 2-methylbenzofuran, and dimethylbenzofurans) are found in various products of coal carbonization: in the gases from coke manufacture,¹⁰⁶ in the naphthalenic^{107,108} (with benzo[b]thiophene) and the phenolic¹⁰⁹ fractions of the tar, and in the products of low-temperature¹¹⁷ and high-temperature^{110–112} carbonization.

Hydroxy derivatives of benzofuran are also found in the phenolic fractions of shale oil tar; such compounds are formed by thermal ring closure of phenol ethers with unsaturated side chains.^{113–115} 2-(4-Methoxyphenyl)benzofuran has been isolated in small amounts from the depolymerization products of some tars (in the presence of phenol).^{114,115}

The higher fractions of coal tar contain polycyclic benzofuran compounds.¹¹⁶ In the fractions with b.p. 311°–314° of the anthracene oil, 1,8-dimethyldibenzofuran (m.p. 87°)¹¹⁷ has been identified, along with two dimethyl isomers of unknown structure (m.p. 45°–46° and 58°–59°); in anthracite tar (b.p. 382°–400°), benzo[b]naphtho[2,1-*d*]furan (**41**) (b.p. 389°, m.p. 103°–104°), benzo[b]naphtho[2,3-*d*]furan (**42**) (b.p. 386°)

¹⁰⁶ P. Hofmann, *Gas Wasserfach* **99**, 301 (1958); *Chem. Abstr.* **52**, 10545 (1958).

¹⁰⁷ B. Iddon and R. M. Scrowston, *Advan. Heterocyclic Chem.* **11**, 178 (1970).

¹⁰⁸ O. Kibino, H. Suzumura, and S. Takeyama, *Koru Taru* **12**, 365 (1960); *Chem. Abstr.* **61**, 2883 (1964).

¹⁰⁹ J. A. Keeble, A. R. Graham, D. C. Quin, D. J. G. Long, and J. R. Nixon, British Patent 865,677 (1961); *Chem. Abstr.* **55**, 21053 (1961).

¹¹⁰ H. Pichler and P. Herrenberger, *Brennst-Chem.* **50**, 341 (1969).

¹¹¹ A. Rutkowski, M. Rutkowski, and Z. Tomasik, *Chem. Stosow., Ser. A* **9**, 111 (1965); *Chem. Abstr.* **63**, 16091 (1965).

¹¹² D. McNeil, *Amer. Chem. Soc., Div. Fuel Chem., Preprints* **7**, 94 (1963); *Chem. Abstr.* **61**, 11811 (1964).

^{113a} K. T. Raudsepp, *Tr. Tallin. Politekh. Inst., Ser. A* **120** (1956); *Chem. Abstr.* **54**, 25705 (1960).

^{113b} K. T. Raudsepp, *Tr. Tallin. Politekh. Inst., Ser. A*, 90 (1955); *Chem. Abstr.* **53**, 4701 (1959).

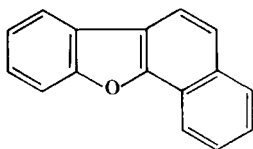
^{113c} K. T. Raudsepp, *Goryuch. Slantsy, Khim. Tekhnol. Sb.*, 107 (1956); *Chem. Abstr.* **54**, 9262 (1960).

¹¹⁴ K. Ouchi and J. D. Brooks, *Nenryo Kyokai-shi* **46**, 895 (1967); *Chem. Abstr.* **70**, 5745 (1969).

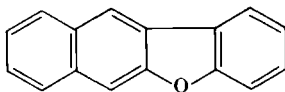
¹¹⁵ K. Ouchi and J. D. Brooks, *Fuel (London)* **46**, 367 (1967); *Chem. Abstr.* **42**, 132 (1968).

¹¹⁶ O. Kruber, A. Raeithel, and G. Grigoleit, *Erdoel Kohle* **8**, 637 (1955); a general survey of the 282 compounds isolated from coal tar.

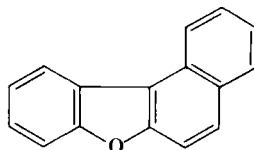
¹¹⁷ O. Kruber and A. Raeithel, *Chem. Ber.* **85**, 327 (1952).



(41)



(42)



(43)

and benzo[*b*]naphtho[1,2-*d*]furan (43)^{118,119} have been separated (with polycyclic benzo[*b*]thiophenes).

Benzofuran derivatives have been found in Texas lignite tars¹²⁰ and in tobacco smoke (benzofuran, methylbenzofuran, dimethylbenzofurans).^{121,122}

B. IN CRUDE PETROLEUM AND IN MINERAL OILS

Benzofuran derivatives are rare in petroleum, where sulfurated heterocycles predominate among heterocyclic compounds. Benzofurans and 2,3-dihydrobenzofurans are found, however, in the 200°–270° fraction of the distillate of California crude oil, with dibenzofurans and naphthobenzofurans.¹²³ Alkyl-dibenzofurans have been traced in the 275°–305° fraction of petroleum with alkynaphthalenes, 4-methyl-dibenzofuran among others.¹²⁴ The distillation of “humic acids” with zinc powder is said to give benzofuran and hydrobenzofuran derivatives.¹²⁵

C. CHARACTERIZATION AND SEPARATION OF BENZOFURAN DERIVATIVES

The characterization of benzofuran and its derivatives in the various fractions of coal tar and petroleum mentioned above utilizes molecular

¹¹⁸ O. Kruber and R. Oberkobusch, *Chem. Ber.* **84**, 831 (1951).

¹¹⁹ O. Kruber and R. Oberkobusch, German Patent 907,895 (1954); *Chem. Abstr.* **52**, 9572 (1958).

¹²⁰ E. J. Kohler, D. C. Rowlands, and W. C. Ellis, *Amer. Chem. Soc., Div. Gas Fuel Chem., Preprints, Apr. 1959* **1**, 81–96; *Chem. Abstr.* **57**, 6233 (1968).

¹²¹ G. Neurath, J. Gewe, and H. Wichern, *Beitr. Tabakforsch.* **4**, 247 (1968); *Chem. Abstr.* **71**, 19642 (1969).

¹²² G. Neurath and M. Duenger, *Beitr. Tabakforsch.* **5**, 1 (1969); *Chem. Abstr.* **72**, 11072 (1970).

¹²³ L. R. Snyder, *Anal. Chem.* **41**, 314 (1969).

¹²⁴ F. F. Hsie Yew and B. T. Mair, *Anal. Chem.* **38**, 231 (1966).

¹²⁵ M. V. Cheshire, P. A. Cranwell, C. P. Falshaw, A. J. Floyd, and R. D. Haworth, *Tetrahedron* **23**, 1669 (1967).

complexes (picrate,^{106,126} 2,4,7-trinitrofluorenone¹²⁴), or chromatographic,¹²⁷⁻¹²⁹ spectrographic,¹³⁰ and polarographic methods.¹³¹

Extraction has been achieved by azeotropic distillation of the benzofuran-indene mixture with diethylene glycol,¹³² through refining with acetonitrile.¹³³ Industrially, benzofuran in the gases from coke manufacture¹³⁴ or from the "crude distilled benzene" fractions¹³⁵ is separated (or eliminated) through refining with sulfuric acid, with formation of "coumarone resins" or "cumar."¹³⁶

"Coumarone resins"¹³⁷ have been the subject of patents, notably for use in building materials¹³⁸ and as protectives in paints and varnishes.¹³⁹ Coumarone-indene (copolymer) resins are also much used: added to rubber, they influence the vulcanizing rate¹⁴⁰ and improve the strength properties of some synthetic rubbers.¹⁴¹⁻¹⁴³ "Coumaronic" derivatives are used for bleaching in the textile industry¹⁴⁴ and as inhibitors in the sulfochlorination of Kogasin.¹⁴⁵

¹²⁶ O. Hibino and H. Suzumura, *Coal Tar* (Tokyo) **7**, 301 (1955); *Chem. Abstr.* **50**, 2147 (1956).

¹²⁷ G. C. Krokel and F. Steinbrecher, *Brennst.-Chem.* **45**, 81 (1966).

¹²⁸ O. Eisen, E. Arumel, J. Eisen, H. Raude, I. Poder, O. Kirret, L. Lahe, and P. M. Vaenikver, *Eesti NSV Tead. Akad. Toim. Fuus. Mat. Tehnika. tead. Seer.* **13**, 135 (1964); *Chem. Abstr.* **62**, 2644 (1965).

¹²⁹ L. Hala, *Chem. Prum.* **18**, 412 (1968); *Chem. Abstr.* **69**, 83193 (1968).

¹³⁰ A. Barton, *C. R. Acad. Sci.* **227**, 342 (1968).

¹³¹ A. G. Pozdeeva and A. G. Volkov, *Zh. Prikl. Khim.* **25**, 1058 (1952); *Chem. Abstr.* **47**, 37162 (1953); *J. Appl. Chem. USSR* **26**, 995 (1953).

¹³² H. G. Franck, *Brennst.-Chem.* **32**, 199 (1951).

¹³³ H. Kowalski, German Patent 1,117,249 (1961); *Chem. Abstr.* **56**, 13164 (1962).

¹³⁴ V. M. Zaichenko, K. A. Belov, and E. M. Sokolova, *Tr. Khar'kov. Politekh. Inst.* **39**, 64 (1962); *Chem. Abstr.* **60**, 11802 (1964).

¹³⁵ F. Breitbach and J. Schmidt (Firma Carl Still), German Patent 1,000,025 (1957); *Chem. Abstr.* **53**, 18451 (1959).

¹³⁶ E. Engel and H. Besdo (Harpener Bergbau AG), German Patent 1,140,200 (1962); *Chem. Abstr.* **58**, 5422 (1963).

¹³⁷ P. Rechner, French Patent 1,359,781 (1964); *Chem. Abstr.* **61**, 11735 (1964).

¹³⁸ M. Inoue, *Coal Tar* (Tokyo) **4**, 326 (1952); *Chem. Abstr.* **47**, 6121 (1953).

¹³⁹ A. L. Rummelsburg, U.S. Patent 2,527,578 (1950); *Chem. Abstr.* **45**, 2234 (1951).

¹⁴⁰ E. Tomczak and M. Gajewski, *Muanyag Gumi* **6**, 403 (1969); *Chem. Abstr.* **72**, 22429 (1970).

¹⁴¹ J. Pielichowski, *Chem. Stosow., Ser. A* **13**, 343 (1970); *Chem. Abstr.* **72**, 101603 (1970).

¹⁴² I. I. Yukel'son, V. V. Legacheva, and I. V. Fedotova, *Koks Khim.* **2**, 34 (1970); *Chem. Abstr.* **72**, 113567 (1970).

¹⁴³ W. J. Wald, U.S. Patent 2,952,662 (1960); *Chem. Abstr.* **55**, 4029 (1961).

¹⁴⁴ T. Sørensen, *Tidsskr. Textiltekn.* **9**, 128 (1951); *Chem. Abstr.* **45**, 10593 (1951).

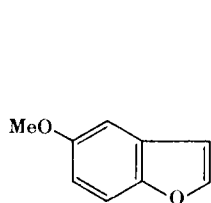
¹⁴⁵ H. Kroepelin, W. Opitz, and W. Freiss, *Erdoel Kohle* **2**, 498 (1949); *Chem. Abstr.* **44**, 2203 (1950).

III. Natural Benzofuran Derivatives

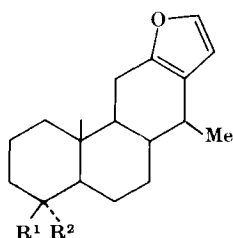
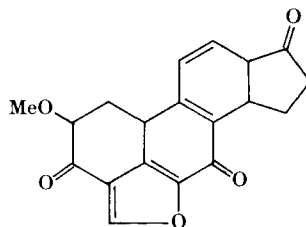
A. GENERAL

While the simultaneous presence of benzofuran and benzothiophene is established in some fractions from coal pyrogenation and from the distillation of some petroleum, benzothiophene is entirely absent in heterocyclic compounds extracted from natural substances of vegetable origin. However, numerous benzofuran or hydrobenzofuran derivatives of biogenetic or metabolic origin have been isolated.

These natural substances range from simple monosubstituted benzofurans, such as 5-methoxybenzofuran (**44**) (which has bactericidal properties^{146,147} and plays an important part in the biosynthesis of natural benzofurans¹⁴⁸) to more complex benzofurans. They include polycyclic compounds with one naphthofuran or phenanthrofurane ring (tanshinones, etc.) and furanic diterpenes¹⁴⁹ [methyl vinhaticoate (**45**), methyl voucapenate (**46**), viridine (**47**)¹⁵⁰⁻¹⁵² (a fungicidal metabolite)].



(44)

(45) R¹ = Me, R² = COOMe(46) R¹ = COOMe, R² = Me

(47)

Examples of polycyclic compounds with several heterocyclic rings include aflatoxin B (**48**)¹⁵³ (2,3,6aα,9aα-tetrahydro-4-methoxycyclopenta[*c*]furo[3',2':4,5]furo[2,3-*h*][1]benzopyran-1,11-dione) which is toxic and carcinogenic, and its metabolite aflatoxin M (**49**)¹⁵⁴ (a toxin of

¹⁴⁶ J. H. Berkinshaw, P. Chaplen, and W. P. K. Findlay, *Biochem. J.* **66**, 188 (1957).

¹⁴⁷ F. M. Dean, "Naturally Occurring Oxygen-Ring Compounds," pp. 135-176. Butterworth, London, 1963.

¹⁴⁸ J. D. Bu'Lock, A. T. Hudson, and B. Kaye, *Chem. Commun.* **16**, 814 (1967); *Chem. Abstr.* **67**, 79047 (1967).

¹⁴⁹ T. A. Spencer, R. A. J. Smith, D. L. Storm, and R. M. Villarica, *J. Amer. Chem. Soc.* **93**, 4856 (1971).

¹⁵⁰ J. F. Grove, P. McCloskey, and J. S. Moffat, *J. Chem. Soc. C*, 743 (1966).

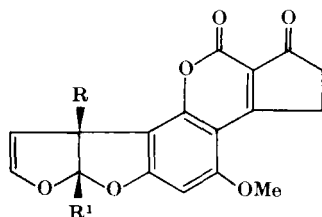
¹⁵¹ M. M. Blight, J. J. W. Coppen, and J. F. Grove, *Chem. Commun.*, 1117 (1968).

¹⁵² S. Neidle and D. Rogers, *J. Chem. Soc., Perkin Trans. 2*, 760 (1972).

¹⁵³ G. Buchi and P. M. Weinreb, *J. Amer. Chem. Soc.* **91**, 5408 (1969).

¹⁵⁴ M. Biollaz, G. Buchi, and G. Milne, *J. Amer. Chem. Soc.* **92**, 1025 (1970).

milk). The presence of the furodihydrobenzofuran system seems necessary for the toxicity to be effective.¹⁵⁵



(48) $R = R^1 = H$

(49) $R^1 = H \quad R = OH$

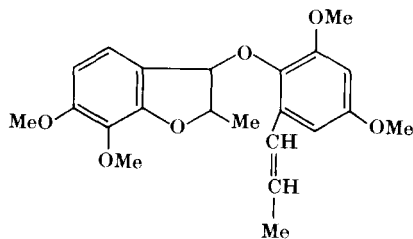
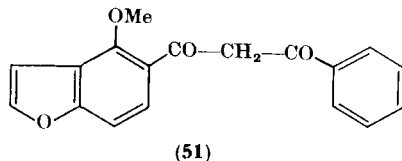
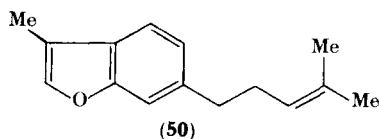
Polyheterocyclic compounds with oxygen and nitrogen heteroatoms include complex alkaloids such as morphine.

Of all these compounds, we consider here only the simple benzofurans.

B. SIMPLE NATURAL BENZOFURANS¹⁵⁶

We mention novel simple benzofurans discovered since Dean's survey¹⁴⁷.

Alkylbenzofurans: furoentalene (50) [6-(4-methyl-3-pentenyl)-3-methylbenzofuran].^{157,158}



(52)

Hydroxybenzofurans: pongamol (51) (5-benzoylacetyl-4-methoxybenzofuran);¹⁴⁷ 5-methoxy-6,7-dimethylbenzofuran, found in tobacco.¹⁵⁹

¹⁵⁵ C. Y. Wang and P. F. Parks, *J. Med. Chem.* **14**, 447 (1971).

¹⁵⁶ W. Karrer, in "Chemische Reihe," Vol. XII. Birkhäuser, Basel, 1958.

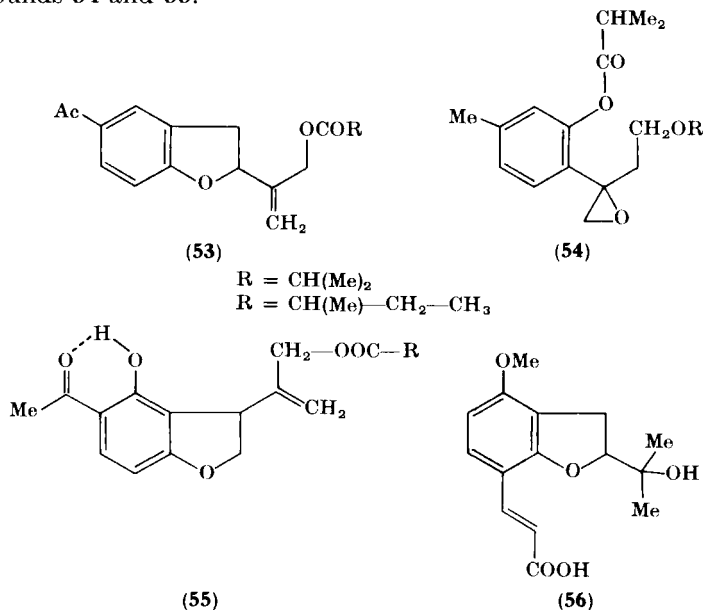
¹⁵⁷ A. J. Weinheimer, F. J. Schmitz, and L. S. Cieresko, *Drugs Sea, Trans. Symp.*, **1967**, 135 (1968); *Chem. Abstr.* **72**, 70562 (1970).

¹⁵⁸ A. J. Weinheimer and P. H. Washeckek, *Tetrahedron Lett.*, 3315 (1969).

¹⁵⁹ A. J. Aasen, B. Kimland, S. O. Almquist, and C. Renzell, *Acta Chem. Scand.* **25**, 3182 (1971).

2,3-Dihydrobenzofurans: eusiderin,¹⁶⁰ supposed to be 3-(6-allyl-2,4-dimethoxyphenoxy)-2,3-dihydro-6,7-dimethoxy-2-methylbenzofuran(52).

Acetyl derivatives: the acetyl derivative with the probable structure 53 (established by means of NMR) has been extracted as a mixture with compounds 54 and 55.¹⁶¹



Benzofuranic acids: *trans*-meranzinic acid (56).¹⁶²

Euparinoid benzofurans: the important class of euparinoids (extracts of plants of the Compositae family), contains benzofurans, dihydrobenzofurans, and also includes compounds with a hydronaphthofuran ring. We mention euparin (the earliest known) (5-acetyl-6-hydroxy-2-isopropenylbenzofuran) (57, $R^6=OH$, $R'=H$);¹⁶³⁻¹⁶⁶ dehydro-tremetone (5-acetyl-2-isopropenylbenzofuran) (57, $R^6=R'=H$);^{167,168}

¹⁶⁰ J. J. Hobbs and F. E. King, *J. Chem. Soc.*, 4732 (1960).

¹⁶¹ F. Bohlmann and C. Zdero, *Tetrahedron Lett.*, 3575 (1970).

¹⁶² P. Venturella, A. Bellino, and M. L. Marino, *Ann. Chim. (Rome)* **59**, 428 (1969).

¹⁶³ Z. Jerzmanowska, *Polska Akad. Umiej. Prace Kom. Farm. Dissert. Pharm.* **3**, 165 (1951); *Chem. Abstr.* **48**, 5848 (1954).

¹⁶⁴ J. Sykulis, *Acta Pol. Pharm.* **15**, 361 (1958); *Chem. Abstr.* **53**, 6536 (1959).

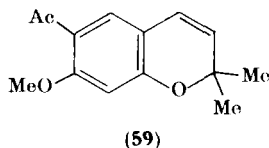
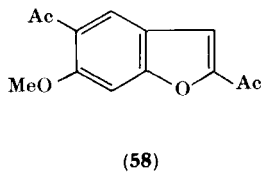
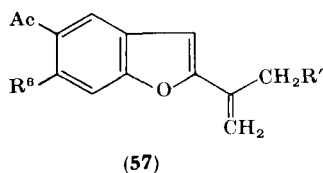
¹⁶⁵ T. Nakaoki, N. Morita, and S. Nishino, *Yakugaku Zasshi* **78**, 557 (1958); *Chem. Abstr.* **52**, 13190 (1958).

¹⁶⁶ S. Sasaki, H. C. Chiang, K. Habaguchi, T. Yamada, K. Nakanishi, S. Matsueda, H. Y. Hsu and W. N. Wu, *Yakugaku Zasshi* **86**, 869 (1966); *Chem. Abstr.* **66**, 499 (1967).

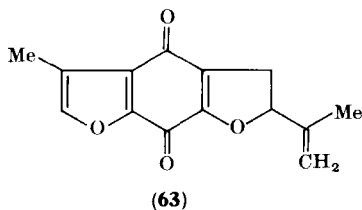
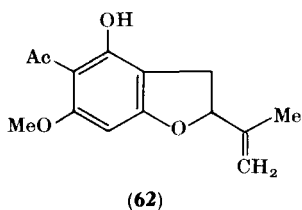
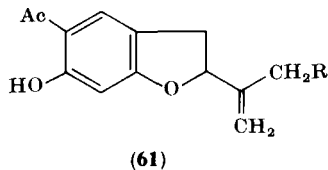
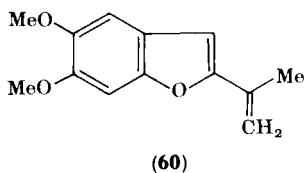
¹⁶⁷ J. I. Degraw and W. A. Bonner, *J. Org. Chem.* **27**, 3917 (1962).

¹⁶⁸ J. I. Degraw, D. M. Bowen, and W. A. Bonner, *Tetrahedron* **19**, 19 (1963).

the structure of which has been confirmed by synthesis;^{34,169} ageratone (57, $R^6=OH$, $R'=OAc$) (2-acetoxyisopropenyl-5-acetyl-6-hydroxybenzofuran);¹⁷⁰ euparone methyl ether (58),¹⁷¹ isolated with encecalin (59), a chromene isomer of euparin methyl ether (57, $R^6=OMe$, $R'=H$) 5,6-dimethoxy-2-isopropenylbenzofuran^{172,173} (60) and 5,6-methylene dioxy-2-isopropenylbenzofuran.¹⁷⁴



Among the *euparinoid 2,3-dihydrobenzofurans*, the main compounds are (-)-tremetone (17a),^{27,168,175,176} toxol (18),^{175,176} hydroxytremetone



¹⁶⁹ P. K. Ramachandran, T. Cheng, and W. J. Horton, *J. Org. Chem.* **28**, 2744 (1963).

¹⁷⁰ T. A. Anthonsen and S. Chantha Rasakul, *Acta Chem. Scand.* **24**, 721 (1970).

¹⁷¹ L. F. Bjeldanes and J. A. Geissman, *Phytochemistry* **8**, 1293 (1969).

¹⁷² T. Murae, Y. Tanahashi, and T. Takahashi, *Tetrahedron*, **24**, 2177 (1968).

¹⁷³ A. R. Alertsén, T. Anthonsen, E. Raknes, and N. A. Sørensen, *Acta Chem. Scand.* **25**, 1919 (1971).

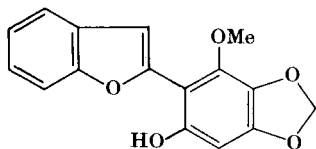
¹⁷⁴ K. Fukui, M. Nakayama, and S. Tanaka, *Bull. Chem. Soc. Jap.* **42**, 1971 (1969).

¹⁷⁵ W. A. Bonner, N. I. Burke, W. E. Fleck, R. K. Hill, J. A. Joule, B. Sjöberg, and J. H. Zalkow, *Tetrahedron* **20**, 1419 (1964).

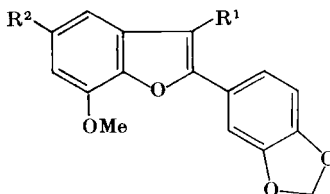
¹⁷⁶ J. H. Zalkow and N. I. Burke, *Chem. Ind. (London)*, 292 (1963).

(**61**, R=H),^{167,177,178} dihydroageratone (**61**, R=OAc).¹⁷¹ Remirol (**62**)¹⁷⁸ and cyperaquinone (**63**)¹⁷⁹ (of which **62** is looked upon as the biogenetic forerunner) have structures related to those of euparinoids.

The final group of natural benzofurans includes the *2-phenylbenzofurans* and *2-phenyl-2,3-dihydrobenzofurans*. 2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)benzofuran (**64**)¹⁴⁷ has recently been isolated from yeast. Other members of the same group recently isolated from various plants are eupomatene (7-methoxy-3-methyl-2-(3,4-methylenedioxyphenyl)-5-*trans*-propenylbenzofuran (**65**);¹⁸⁰ egonol (**66**),^{147,181-184}



(64)

(65) R¹ = Me R² = -CH=CH-Me(66) R¹ = H R² = (CH₂)₃-OH

which has a closely related structure and is in some cases¹⁸² accompanied by a similar compound, 2-(3,4-dimethoxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran; pterofuran (**67**)^{185,186} (2-(2,4-dimethoxy-3-hydroxyphenyl)-6-hydroxybenzofuran), a probable intermediate of coumestan-type compounds.

Among the 2-phenyl-2,3-dihydrobenzofurans, noteworthy are (+)obtusofuran (**68**) with 2*R*,3*R* configuration,¹⁸⁷ and melanoxin (**69**) (2,3-dihydro-5-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-6-methoxy-3-methylbenzofuran) with 2*S*,3*S* configuration.¹⁸⁸ Compounds with structures closely related to that of (**69**) have been isolated from the

¹⁷⁷ P. Gerike, Ph. D. Thesis Salt Lake City Univ., 1966; *Diss. Abstr.* **26**, 6370 (1966).

¹⁷⁸ I. Harada, Y. Hirose, and M. Nakazaki, *Tetrahedron Lett.*, 5463 (1968).

¹⁷⁹ R. A. Allan, R. L. Correll, and R. J. Wells, *Tetrahedron Lett.*, 4669 (1969).

¹⁸⁰ R. S. McCredie, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.* **22**, 1011 (1969).

¹⁸¹ C. Y. Hopkins, D. F. Ewing, and M. J. Chisholm, *Can. J. Chem.* **45**, 1423 (1967).

¹⁸² R. Segal, I. Milo-Goldzweig, S. Sokoloff, and D. V. Zaitschek, *J. Chem. Soc. C*, 2402 (1967).

¹⁸³ M. Matsubara, *Nippon Nogei Kagaku Kaishi* **41**, 304, (1967).

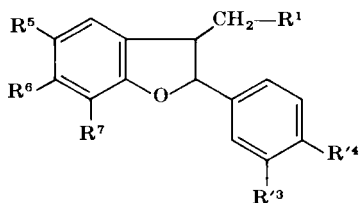
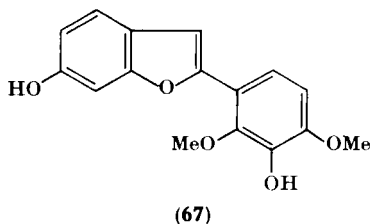
¹⁸⁴ E. Ritchie and W. C. Taylor, *Aust. J. Chem.* **22**, 1329 (1969).

¹⁸⁵ R. G. Cooke and I. D. Roe, *Aust. J. Chem.* **17**, 378 (1964).

¹⁸⁶ R. G. Cooke and R. M. MacQuillin, *Aust. J. Chem.* **22**, 2395 (1969).

¹⁸⁷ M. Gregson, W. D. Ollis, B. T. Redman, and I. O. Sutherland, *Chem. Commun.*, 1394 (1968).

¹⁸⁸ B. J. Donnelly, D. M. X. Donnelly, A. M. O'Sullivan, and J. P. Prendergast, *Tetrahedron* **25**, 4409 (1969).



(68) $R^1 = H$, $R^5 = OH$, $R^3 = R^4 = H$,
 $R^6 = OMe$, $R^7 = H$

(69) $R^1 = H$, $R^5 = OH$, $R^3 = OH$,
 $R^4 = R^6 = OMe$, $R^7 = H$

(70) $R^1 = OH$, $R^5 = CH=CH-CH_2OH$,
 $R^7 = R^3 = OMe$, $R^4 = OH$, $R^6 = H$

treatment products of lignin,^{189,190} for which a 2,3-dihydro-2-phenylbenzofuran structure is assumed.¹⁹¹

Finally, there were recently isolated an optically active phenolic compound, dehydrodiconiferyl alcohol (2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropenyl)-7-methoxy-3-benzofuranyl-methanol) (70),¹⁹² and a complex 2,3-dihydro-2-phenylbenzofuran, hordanatin A, an antifungal factor;¹⁹³ it has recently been synthesized,¹⁹⁴ and may play a part in the lignification process.

IV. General Methods of Synthesis of Benzofurans

The numerous syntheses of the benzofuran ring may be classified under four headings:

- A. Formation of the heterocyclic ring from an aromatic substrate
- B. Formation of the heterocyclic ring from a nonaromatic substrate
- C. Fusion of the benzene ring to a furan substrate
- D. Formation of the heterocyclic ring from other heterocyclic compounds.

A. FORMATION OF THE HETEROCYCLIC RING FROM AN AROMATIC SUBSTRATE

These methods involve the ring-closure, cyclodehydration, heterocyclic ring closure, and intramolecular condensation of suitable aromatic compounds.

¹⁸⁹ G. Gellerstedt and J. Gierer, *Acta Chem. Scand.* **22**, 2029 (1968).

¹⁹⁰ H. Hatakeyama, J. Nakano, A. Hatano, and N. Migita, *Tappi* **52**, 1724 (1969); *Chem. Abstr.* **72**, 4447 (1970).

¹⁹¹ E. Alder, S. Delin, and K. Lundquist, *Acta Chem. Scand.* **13**, 2149 (1959).

¹⁹² K. Weinges, R. Mueller, P. Klass, and H. Jaggy, *Justus Liebigs Ann. Chem.* **736**, 770 (1970).

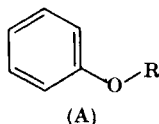
¹⁹³ A. Stoessl, *Can. J. Chem.* **45**, 1745 (1967).

¹⁹⁴ A. Stoessl, U.S. Patent 3,475,459 (1969); *Chem. Abstr.* **73**, 14665 (1970).

1. General

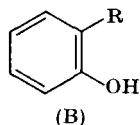
The syntheses of benzofurans utilize many classical and long-known reactions. The literature on the subject is fairly scattered. Monographs¹⁻³ and some more general texts¹⁹⁵⁻¹⁹⁷ review these methods, which can be classified under three main headings (the reaction mechanisms may differ within each group):

Group 1: the starting molecule is of type A. This group mainly



includes aryloxyated compounds: aryloxyacetaldehydes, aryloxyacetones, aryloxyacetic acids, which can be subjected to thermal or chemical cyclodehydration. The group includes reactions starting from a complex molecule of the same type, akin to the Fischer indole synthesis.

Group 2: the starting molecule is of type B. This group includes



substituted phenolic compounds, where R is a saturated or unsaturated alkyl radical. The benzofuran molecule can be formed by various methods:

Method a: Hydroxylated allyl compounds (which can be obtained from allyloxy compounds of type A by Claisen rearrangement¹⁹⁸) form benzofurans or 2,3-dihydroxybenzofurans by ring closure.

Method b: Compounds B with a side-chain R of the type COCH_2X ($\text{X} = \text{Cl}$ or Br) (formed by a Hoesch condensation¹⁹⁹ or Fries rearrangement²⁰⁰ from a corresponding molecule of type A) result in 3(2*H*)-benzofuranones (von Auwers-Shriner-Anderson reaction).

Method c: If the side chain R is of the $\text{CH}_2\text{-CO-R}$ type, the benzo-

¹⁹⁵ A. L. Mndzhoyan, "Synthesis of Heterocyclic Compounds," Vol. II. Chapman & Hall, London, 1959.

¹⁹⁶ J. Mathieu, A. Allais, and J. Valls, "Cahiers de Synthèse Organique," Masson Paris, 1962, Vol. IX, X; 1966, Vol. XII, 1961, Vol. VII.

¹⁹⁷ A. R. Katritzky and J. M. Lagowski, "Principles of Heterocyclic Chemistry." Methuen, London, 1966.

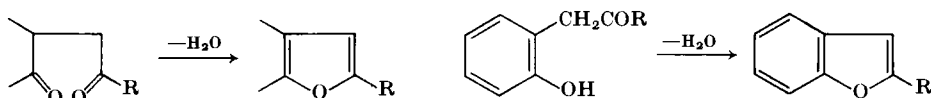
¹⁹⁸ D. S. Tarbell, *Org. React.* **2**, 1 (1944).

¹⁹⁹ P. E. Spoerri and A. S. Dubois, *Org. React.* **5**, 387 (1949).

²⁰⁰ H. H. Blatt, *Org. React.* **1**, 342 (1942).

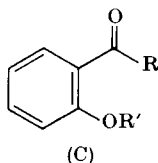
furane ring is formed by cyclodehydration, as in the Paal method (1884) for the synthesis of furans by dehydration of 1,4-dicarbonyl compounds.²⁰¹

This occurs for 2-hydroxyphenylacetones, hydroxylated deoxybenzoins, and, as in the simplest case ($R=H$), *o*-hydroxyarylacetaldehydes. The reaction is especially suitable for the synthesis of polyheterocyclic compounds with fused benzofuran rings.



Ring-closing dehydration, with fission or heterocyclic ring closures using pyridine hydrochloride,^{202,203} or boron trichloride²⁰⁴ may be used for the preparation of molecules from types A and B.

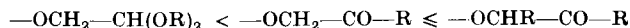
Group 3. the starting molecule is of type C. This group includes



hydroxylated carbonyl compounds with reactive methylene groups, and the ring-closure reaction is an intramolecular condensation.

2. Cyclodehydration of Aryloxy Derivatives (Group 1)

a. *Cyclodehydration of Aryloxyaldehydes.* Ring-closing dehydration of aryloxyacetaldehydes or of their acetals (71) (obtained from the appropriate phenol and a halogenated acetaldehyde dialkyl acetal), according to Stoermer,² gives the highest yields of all the reactions in this group. The yields vary within a given series according to the following sequence:



The Pomeranz-Fritsch method (boron trifluoride + trifluoroacetic anhydride) is not suitable;²⁰⁵ but polyphosphoric acid (PPA) at 100°

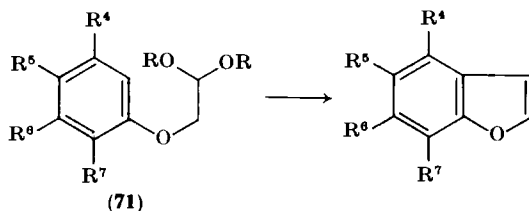
²⁰¹ R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron* **2**, 203 (1957).

²⁰² R. Royer and P. Demerseman, *Bull. Soc. Chim. Fr.*, 2633 (1968).

²⁰³ R. Royer and P. Demerseman, *Symp. Heterocycl. Comp.*, 3rd, 1969.

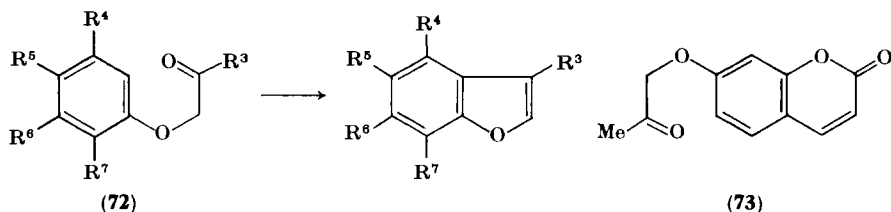
²⁰⁴ F. M. Dean, J. Goodchild, L. Houghton, J. A. Martin, B. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 4153 (1966).

²⁰⁵ M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Off, *Tetrahedron* **27**, 1255 (1971).



or P₂O₅ give satisfactory yields. Several benzofurans unsubstituted in the heterocyclic ring have been prepared in this way.²⁰⁶⁻²⁰⁷

b. *Cyclodehydration of Aryloxyacetones.* Cyclodehydration of aryloxyacetones (72) (from the corresponding phenols and halogenoacetones), which has been comparatively little investigated, leads to 3-alkylbenzofurans.^{10,208-212} The most frequently used dehydrating media are sulfuric acid, zinc chloride, phosphorus oxychloride, and PPA.



Monoacetonylethers of resorcinol ring close with particular ease:²¹⁰ when preparing 3-hydroxyphenoxyacetone (72, R⁶ = OH, R³ = Me), 6-hydroxy-3-methylbenzofuran was isolated.²¹⁰ Systematic investigation of ethers of this type (72, R⁶ = OH, R⁴ = R, R³ = Me) has evidenced the general character of this dehydration reaction with alkaline catalysts (0.1 N KOH); methylation of the hydroxyl group inhibits the reaction.²¹¹

With the acetonylether of 7-hydroxycoumarin (73), the reaction gives 3-methylpsoralene; cyperaquinone (63) is synthesized by the same method.²¹¹ Polysubstituted psoralenes have also been obtained from polyalkylated acetonylethoxycoumarins, for instance, 6-ethyl-3,5,9-trimethylpsoralene from 7-acetonylethoxy-4,8-dimethyl-3-ethylcoumarin.⁷⁶

c. *Cyclodehydration of 3-Aryloxy-2-Butanones and of Aryloxyketones Generally.* 3-Aryloxy-2-butanones (74) are obtained from the appro-

^{206a} P. Sigwalt, *J. Polym. Sci.* **52**, 15 (1961).

^{206b} P. Sigwalt, *C. R. Acad. Sci.* **252**, 3800 (1961).

²⁰⁷ P. Spagnolo, M. Tiecco, A. Tundo, and G. Martelli, *J. Chem. Soc., Perkin Trans. I*, 556 (1972).

²⁰⁸ R. Royer and E. Bisagni, *Bull. Soc. Chim. Fr.*, 521 (1959).

²⁰⁹ H. Singh and J. C. Verma, *J. Indian Chem. Soc.* **40**, 31 (1963).

²¹⁰ K. Raudsepp and H. Kippze, *Tr. Tallin. Politekh. Inst., Ser. A*, **216**, 79 (1964).

²¹¹ J. K. McLeod and B. R. Worth, *Tetrahedron Lett.*, 237, 241 (1972).

²¹² J. N. Chatterjea, *J. Indian Chem. Soc.* **30**, 1 (1953).

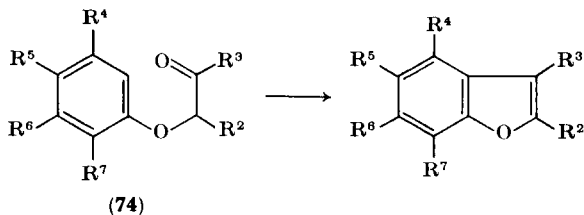
priate phenol and 3-chloro-2-butanone. This method is the best and quickest for preparing 2,3-dialkylbenzofurans.

The dehydrating media are usually those suitable for aryloxyketones. In the case of Bz-methoxylated 2,3-dialkyl derivatives, POCl_3 is the best dehydrating medium. Various reagents, such as H_2SO_4 , BF_3 , TiCl_4 , PPA, have been used in the case of carboxyl derivatives [ring closure of 3-(4-carbomethoxyphenoxy)-2-butanone].

Numerous derivatives of (1) have been thus prepared, notably 2,3-dimethyl (or dialkyl)benzofurans Bz-substituted by alkyl radicals,^{36,213-218} methoxyl groups,^{101,219-221} halogen atoms,^{217,222-224} aryl groups,²²⁵ acetyl groups,^{215,218,226} formyl groups,^{222,226} and carboxyl groups.^{226,227} The method is especially valuable in the case of formyl derivatives, which are difficult to obtain otherwise.

In general, the ring closure of 3-substituted ketones ($\text{R}^6 \neq \text{H}$) gives a mixture of isomeric benzofurans. The orientation of the ring closure depends on the nature of the substituent and of the cyclizing medium.²²⁷ It is difficult to give a rule according to the electronic effects of the R^6 substituent: electron withdrawing R^6 (COOMe ,^{226,227} NO_2 ²²⁶) should favor the formation of the benzofuran substituted in the 4 position by the R^6 group, although the acetyl group gives the 6-acetyl isomer.²²⁶

- ²¹³ T. K. Veselovskaya, I. V. Machinskaya, and H. J. Nadelyaeva, *Zh. Obshch. Khim.* **34**, 560 (1964); *Chem. Abstr.* **60**, 13218 (1964).
- ²¹⁴ D. S. Tarbell, R. M. Carman, D. D. Chapman, S. E. Cremer, A. D. Cross, K. R. Huffman, M. Kunstmann, N. J. McCorkindale, J. G. McNally, J. A. Rosowsky, L. Varino, and R. L. West, *J. Amer. Chem. Soc.* **83**, 3096 (1961).
- ²¹⁵ R. Royer, M. Hubert-Habart, L. René, A. Cheutin, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 1259 (1964).
- ²¹⁶ R. Royer and L. René, *Bull. Soc. Chim. Fr.*, 1036 (1970).
- ²¹⁷ E. Bisagni, J. P. Marquet, A. Cheutin, and R. Royer, *Bull. Soc. Chim. Fr.*, 1466 (1965).
- ²¹⁸ P. Demerseman, J. P. Lechartier, C. Pène, A. Cheutin, R. Royer, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 1473 (1965).
- ²¹⁹ R. Royer, E. Bisagni, C. Hudry, A. Cheutin, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 1103 (1963).
- ²²⁰ D. J. S. Beer, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 1262 (1953).
- ²²¹ P. P. Brust, Ph. D. Thesis, Univ. Rochester, New York, 1965.
- ²²² G. Goldenberg, F. Binon, and E. Gillyns, *Chim. Ther.*, 221 (1966).
- ²²³ C. Pène, P. Demerseman, A. Cheutin, and R. Royer, *Bull. Soc. Chim. Fr.*, 586 (1966).
- ²²⁴ R. Royer and L. René, *Bull. Soc. Chem. Fr.*, 3601 (1970).
- ²²⁵ P. Demerseman, J. Guillaumel, A. Cheutin, and R. Royer, *Bull. Soc. Chim. Fr.*, 2253 (1970).
- ²²⁶ Y. Kawase, M. Takashima, *Bull. Chem. Soc. Jap.* **40**, 1224 (1967); *Chem. Abstr.* **67**, 82013 (1967).
- ²²⁷ S. Yamaguchi, S. Kuroda, and Y. Kawase, *Nippon Kagaku Zasshi* **92**, 95 (1971); *Chem. Abstr.* **76**, 25032 (1972).

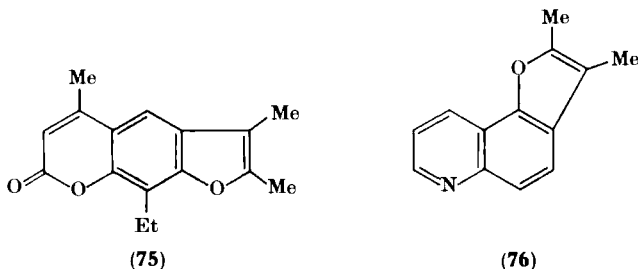


With an electron-donor R^6 , a mixture of the 4- and 6-substituted isomers is formed.

The yields also depend on the ring-closing medium. In the series of the Bz-acetylated ketones, they seem to be higher when R^7 = isopropyl.

The method has also proved to be applicable to the synthesis of polycyclic benzofurans: naphthofurans from suitable naphthols,²¹⁵ benzodifurans from Bz-hydroxybenzofurans,²¹⁹ naphthodifurans from hydroxylated naphthofurans,²²⁸ thienobenzofurans from Bz-hydroxybenzo[*b*]thiophenes.^{218,229}

3-Coumarinyloxy-2-butanones, obtained from suitable Bz-hydroxycoumarins, can be dehydrated (with H_2SO_4) to furocoumarins (e.g., 8-ethyl-7-hydroxy-4-methylcoumarin gives 9-ethyl-2,3,5-trimethyl-7H, furo[3,2-*g*][1]benzopyran-7-one (75)).²³⁰



2,3-Dimethylbenzofuran derivatives can also be obtained from hydroxylated nitrogen heterocycles: Bz-hydroxyquinolines readily give 3-quinolyloxy-2-butanones, which undergo ring-closing dehydration in good yields (e.g., 70% of 2,3-dimethylfuro[2,3-*f*]quinoline (76) is obtained).²²³ On the other hand, although Py-hydroxylated quinolines do give the corresponding 3-substituted 2-butanones, the latter are resinified by dehydrating media.²³¹

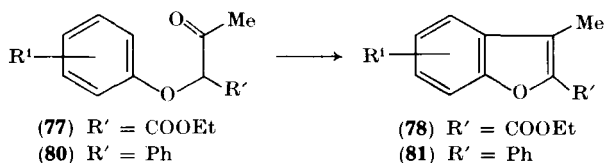
²²⁸ R. Royer, E. Bisagni, M. Hubert-Habart, L. René, and J. P. Marquet, *Bull. Soc. Chim. Fr.*, 1794 (1965).

²²⁹ R. Royer, P. Demerseman, and J. P. Lechartier, *C. R. Acad. Sci.* **254**, 2605 (1962).

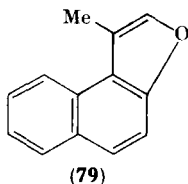
²³⁰ J. P. Lechartier, P. Demerseman, A. Cheutin, and R. Royer, *Bull. Soc. Chim. Fr.*, 1716 (1966).

²³¹ R. Royer, P. Demerseman, C. Pène, and C. Colin, *Bull. Soc. Chim. Fr.*, 915 (1967).

Related methods. The replacement of 3-chloro-2-butanone (or of similar α -halogenated ketones) by ethyl α -chloroacetoacetate [Graffenried and Kostanecki, 1910] gives aryloxyacetoacetates (77). Cyclodehydration of esters (77) (with H_2SO_4) gives good yields (60–70%) of coumarilic esters (78),²³² which are sometimes difficult to synthesize by other methods.



Various 3-methylcoumarilic acids substituted in the benzene ring by alkyl or methoxyl groups have been thus prepared, then decarboxylated to the corresponding benzofurans,^{10,208} e.g., 3-methyl-4,7-dimethoxybenzofuran; 2-naphthol²³³ leads to 3-methylnaphtho[2,1-*b*]furan (79), guaiacol to ethyl 7-methoxy-3-methyl coumarilate.²³⁴



Condensing α -brominated phenylacetones with alkali-metal phenates gives α -(*R*-substituted phenoxy)- α -phenylacetones (80). 3-Methyl-2-phenylbenzofurans²³⁵ (81, $\text{R}=\text{H}$) and 6-methoxy-3-methyl-2-phenylbenzofurans²³⁶ are thus obtained (with H_2SO_4). Novel rearrangements occur in some cases.^{237–239}

d. *Cyclodehydration of Aryloxyacetophenones, α -Aryloxypropiophenones, and α -Aryloxydeoxybenzoines.* Aryloxyacetophenones (82, $\text{R}^2 = \text{H}$). Condensation of aromatic hydroxylated compounds (simple or fused) with phenacyl halides ($\text{Ar}-\text{CO}-\text{CH}_2\text{X}$) readily gives aryloxyacetophenones (82, $\text{R}^2 = \text{H}$), the cyclodehydration of which *in principle* gives

²³² W. E. Boehme, *Org. Syn.*, **33**, 43 (1953).

²³³ E. I. du Pont de Nemours, British Patent 705,950 (1954); *Chem. Abstr.* **49**, 2233 (1955).

²³⁴ B. Sila, *Rocz. Chem.* **42**, 553 (1968).

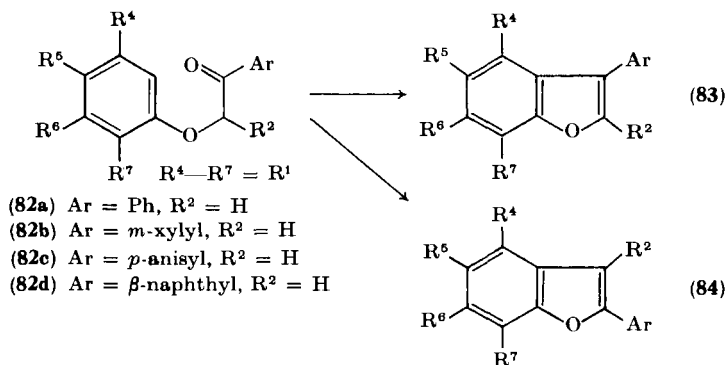
²³⁵ H. Fieselmann and J. Ribka, *Chem. Ber.* **89**, 140 (1956).

²³⁶ D. Mohlo and C. Mentzer, *C. R. Acad. Sci.* **223**, 333 (1946).

²³⁷ W. Davies and S. Middleton, "Current Trends in Heterocyclic Compounds," Proc. Canberra Symp., 1957. Academic Press, New York, 1958.

²³⁸ W. Davies and S. Middleton, *Chem. Ind. (London)*, 1999 (1957).

²³⁹ W. Davies and S. Middleton, *J. Chem. Soc.*, 822 (1958).



3-arylbenzofurans (83) (Table I). Actually, many instances of rearrangement leading to 2-arylbenzofurans have been observed (Table I) depending on the conditions [structure of ketone (82), medium, temperature]. Thus, for 82a (R¹ = R² = H), PPA at 80° gives the normal 3-aryl compound, at 80°–130° a mixture of 2-aryl and 3-aryl isomers, at 130°–135° the 2-aryl isomer alone.²³⁸ This rearrangement is not restric-

TABLE I
CYCLODEHYDRATION OF ARYLOXYACETOPHENONES
AND α -ARYLOXYPROPIOPHENONES

Starting compound	Benzofurans	Reagents	References
(82a) R ¹ = <i>o</i> -Me, R ² = H	2-Phenyl 7-Me ^a	PPA 140°	239
(82a) R ¹ = <i>m</i> -Me, R ² = H	2-Phenyl-6-Me ^a	PPA 140°	239
(82a) R ¹ = <i>p</i> -Me, R ² = H	2-Phenyl 5-Me ^a	PPA 140°	239
(82a) R ¹ = <i>p</i> -Me, R ² = H	3-Phenyl 5-Me	P ₂ O ₅ , reflux benzene	243
(82a) R ¹ = <i>o(m,p)</i> OMe, R ² = H	2-Phenyl 7(6,5)-OMe ^a	PPA 132°	242
(82a) R ¹ = <i>o(m,p)</i> OMe, R ² = H	3-Phenyl 7(6,5)-OMe	PPA 80°	241
(82a) R ¹ = H, R ² = H	3-Phenyl + 2-phenyl ^b	P ₂ O ₅ , reflux benzene	243
(82a) R ⁴ = Me, R ⁷ = isoPr, R ² = H	3-Phenyl 4-Me 7-isoPr	H ₂ SO ₄ + CH ₃ COOH	208,244
(82a) R ⁶ = OH(OMe), R ² = H	3-Phenyl 6-OH	Pyridine HCl	245
(82a) R ⁶ = O-CH ₂ -CO-Ph	3-Phenyl 6-OH	Pyridine HCl	245
(82a) R ⁶ = OMe, R ² = Me	2-Me 3-phenyl 6-OH	Pyridine HCl	245
(82a) R ⁵ = Cl(Br), R ² = Me	2-Me 3-phenyl 5-Cl(Br)	PPA	245
(82b) R ¹ = <i>o(m,p)</i> -Me, R ² = H	2- <i>m</i> -Xylyl 7(6,5)-Me ^a	PPA 130°	240
(82c) R ¹ = H, R ² = H	2(3)- <i>p</i> -anisyl ^a	P ₂ O ₅ , xylene	242
(82c) R ⁵ = Ac, R ² = Me	2-Me 5-Ac 3- <i>p</i> -anisyl	PPA 130°	101
(82d) R ¹ = H	2-(2-Naphthyl) ^a	PPA 140°	246

^a Rearrangement.

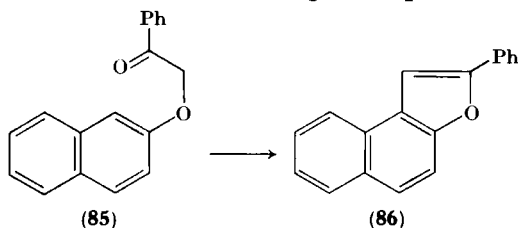
^b Trace only.

ted to 3-phenyl derivatives, but also applies to 3-methyl-, 3-*t*-butyl- and 3-benzylbenzofurans.²⁴⁷⁻²⁴⁹

The introduction of a *p*-methoxyl group on the phenacyl residue (**82c**, $R^1 = R^2 = H$) allows a lower temperature, about 70°, for dehydration by PPA and facilitates rearrangement to 2-(4-methoxyphenyl)benzofuran. If $R^5 = OMe$ in (**82c**), the yield is lowered to 10%. If $R^7 = OMe$ in (**82c**), the yield is zero both at 80° and at 130°.²⁴⁷

To obtain 3-aryl compounds free from 2-aryl isomers, several methods have been used: reflux in benzene with P_2O_5 ,²⁵⁰ heating with $H_2SO_4 + MeCOOH$,^{208,245} and heating with pyridine hydrochloride.²⁴⁵

For naphthoxyacetophenones [e.g., ketone (**85**)], PPA gives 2-phenylnaphtho[2,1-*b*]furan (**86**), whether at 80° or at 132°. This shows the influence not only of the temperature, but also of the structure of the starting acetophenone,²⁴¹ on the rearrangement process.



α -Aryloxypropiofenones (**82**, $R^2 = Me$). This reaction gives, without rearrangement, exclusively the expected 2-methyl-3-phenylbenzofurans (**83**, $R = Me$) in dehydrating media ($POCl_3$, H_2SO_4 , PPA at 130°). A range of 2-methyl-3-phenylbenzofurans with various substituents have thus been synthesized.¹⁰¹ α -1-Naphthoxypropiofenones and α -2-naphthoxypropiofenones also give the expected disubstituted naphthofurans.²⁵¹

²⁴⁰ R. Klink and K. H. Baron (Merck Co.), British Patent 1,114,030 (1968); *Chem. Abstr.* **69**, 19008 (1968); U.S. Patent 3,449,914 (1970); *Chem. Abstr.* **72**, 121353 (1970).

²⁴¹ K. K. Thomas and M. M. Bokadia, *J. Indian Chem. Soc.* **43**, 713 (1966).

²⁴² R. Royer, P. Demerseman, and E. Bisagni, *Bull. Soc. Chim. Fr.*, 685 (1960).

²⁴³ J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.* **40**, 144 (1963).

²⁴⁴ R. Royer and E. Bisagni, *Helv. Chim. Acta* **42**, 2364 (1959).

²⁴⁵ R. Royer and C. Hudry, *Bull. Soc. Chim. Fr.*, 939 (1961).

²⁴⁶ J. N. Chatterjea, N. M. Sahai, and N. C. Jain, *J. Indian Chem. Soc.* **47**, 261 (1970).

²⁴⁷ K. K. Thomas and M. M. Bokadia, *J. Indian Chem. Soc.* **45**, 265 (1968).

²⁴⁸ W. Davies and S. Middleton, *J. Chem. Soc.*, 3544 (1959).

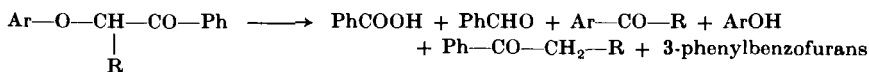
²⁴⁹ A. N. Kost, V. A. Budylin, D. O. Sterligov, and E. D. Matveievna, *Zh. Org. Khim.* **6**, 1503 (1970); *Chem. Abstr.* **73**, 98705 (1970).

²⁵⁰ J. N. Chatterjea, *Sci. Cult.* **24**, 40 (1958); *Chem. Abstr.* **52**, 10048 (1959).

²⁵¹ R. Royer, E. Bisagni, and C. Hudry, *Bull. Soc. Chim. Fr.*, 1178 (1960).

α -Aryloxydeoxybenzoins (**82**, $R^2 = \text{Ph}$). Cyclodehydration with PPA of α -aryloxydeoxybenzoins (obtained by condensation of an α -brominated deoxybenzoin with an alkali metal phenate) gives, in 75–95% yields, substituted (5-methyl, 6,7-dimethyl, 5,7-dimethyl, 4,7-dimethyl, 6,7-dimethoxy) 2,3-diphenylbenzofurans (**83**, $R^2 = R^3 = \text{Ph}$).²⁵²

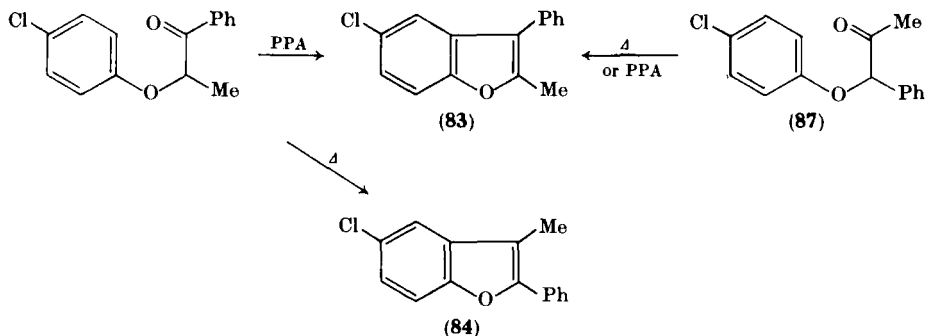
e. *Pyrolysis of Aryloxyacetophenones and of α -Aryloxypropiophenones.* Aryloxyacetophenones (**82**, $R^2 = \text{H}$) (e.g., **82a**, $R^4 = \text{Me}$, $R^7 = \text{isoPr}$, $R^2 = \text{H}$) and α -aryloxypropiophenones (**82**, $R^2 = \text{Me}$) cannot be distilled under atmospheric pressure without undergoing pyrolysis, which leads to a complex mixture of cracking and ring-closed dehydration products.^{244,253,254}



The cyclization is therefore a low-yield secondary reaction and not a useful route to 3-phenyl benzofurans. α -Phenoxypropiophenones and α -(3-methoxyphenoxy)acetophenones give fission products only.²⁵¹ Benzofuryl-Bz-oxyacetophenones yield 5% of furobenzofurans only.²⁵⁵ α -(3-Methoxyphenoxy)propiophenones resist thermal cracking under the same conditions.²⁴⁵

Rearrangements have also been observed in such thermolyses.²⁵⁶ Thus, α -(4-chlorophenoxy)propiophenone, dehydrated with PPA, gives exclusively the corresponding 3-phenylbenzofuran (**83**, $R^2 = \text{Me}$, $R^5 = \text{Cl}$) in 91% yield; thermolysis gives the isomeric 2-phenylbenzofuran (**84**, $R^3 = \text{Me}$) (4% yield).

Cyclodehydration of 1-[4-chloro(or bromo)phenoxy]-1-phenylacetones (**87**) gives benzofurans (**83**)²⁵⁶ with rearrangement, both with chemical



²⁵² C. Perrot and E. Cerutti, *C. R. Acad. Sci., Ser. C* **264**, 1301 (1967).

²⁵³ R. Royer and E. Bisagni, *Chimia* **13**, 335 (1959).

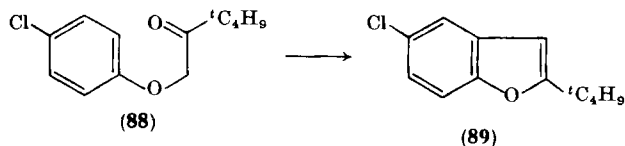
²⁵⁴ R. Royer and E. Bisagni, *Bull. Soc. Chim. Fr.*, 1468 (1959).

²⁵⁵ R. Royer, J. L. Derocque, P. Demerseman, and A. Cheutin, *C. R. Acad. Sci., Ser. C* **262**, 1282 (1966).

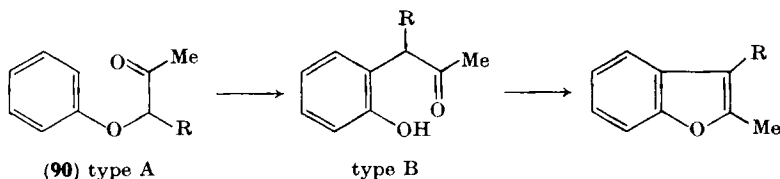
²⁵⁶ E. Bisagni and C. Rivalle, *Bull. Soc. Chim. Fr.*, 2463 (1969).

reagents and by thermolysis (43% yield). The rearrangement has been observed when starting from α -1(or 2)-naphthoxypropiophenones: thermolysis gives (in 20% yields) different naphthofurans from those obtained by normal cyclodehydration (P_2O_5 in xylene).²⁵¹

Thermal ring closure of α -(4-chlorophenoxy)pinacolone (88) gives 5-chloro-2-*t*-butylbenzofuran (89) by a similar rearrangement.²⁵⁷

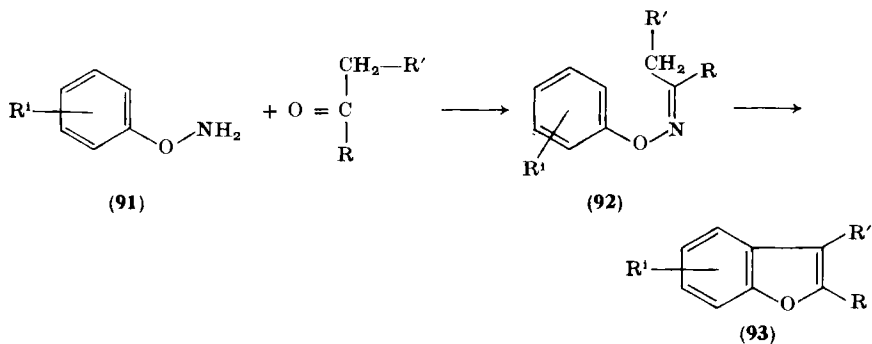


f. *Photochemical Ring Closure of α -Aryloxyketones.* By irradiation at room temperature, a molecule of type A forms an intermediate type B, and then a benzofuran derivative by heterocyclic ring closure. Thus, aryloxyacetones (90) irradiated in methanol give the corresponding 2-methylbenzofurans.^{258,259} With Br or NO_2 as *meta*-substituents, the



reaction of ketones (90) is delayed or inhibited. In some cases, the dimethyl acetal of ketone (90) is isolated. Naphthofurans have also been prepared in this way,²⁶⁰ in low yields.

g. *Synthesis of Benzofurans from O-Aryloximes.* This novel method, discovered in 1966 by Sheradsky,²⁶¹ has proved fruitful for the synthesis



²⁵⁷ E. Bisagni and C. Rivalle, *Bull. Soc. Chim. Fr.*, 3111 (1969).

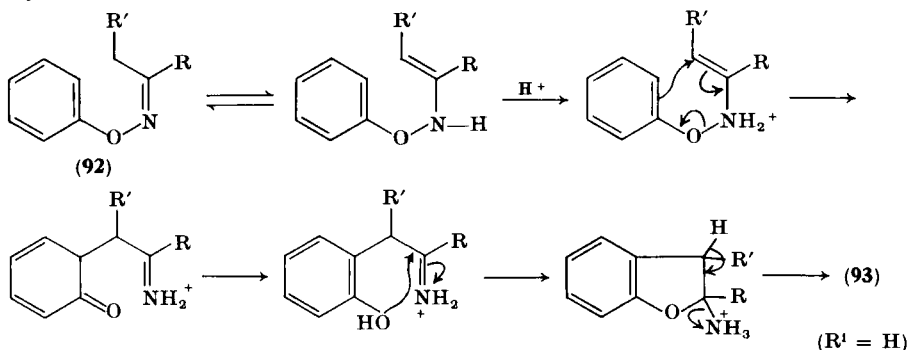
²⁵⁸ J. Hill, *Chem. Commun.*, 260 (1966).

²⁵⁹ M. K. M. Dirania and J. Hill, *J. Chem. Soc. C*, 1311 (1968).

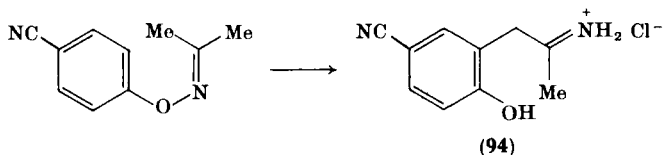
²⁶⁰ J. R. Collier, M. K. M. Dirania, and J. Hill, *J. Chem. Soc. C*, 155 (1970).

²⁶¹ T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966).

of simple or fused benzofurans. O-Phenyloximes (92), obtained from mixtures of phenoxyamines (91) and suitable ketones, heated in acetic acid with BF_3 etherate, give substituted benzofurans (93) in good yields. The reaction mechanism²⁶³ is similar to that of the Fischer



indole synthesis.²⁶² In some cases salts of O-hydroxyarylketimines (94)



have been detected.²⁶⁴ Yields are high: 2-methylbenzofurans, 2-phenylbenzofurans, as well as 1,2,3,4-tetrahydrodibenzofuran (93, $\text{R} + \text{R}' = (\text{CH}_2)_4$, $\text{R}^1 = \text{H}$), have been obtained in 71%, 92%, and 74% yields, respectively.²⁶¹

O-Aryloximes may also be prepared from an aryl halide activated by an electron-withdrawing group [*o*(or *p*)-bromo(or fluoro)nitrobenzene derivatives] and metal salts of oximes. Such compounds (92) readily undergo ring closure on heating in ethanolic hydrochloric acid, and give the corresponding benzofurans in good yields (65–100%).^{265–267}

Numerous polysubstituted benzofurans have thus been prepared,^{261,262,267,268} particularly nitro derivatives, some of which show anti-inflammatory and antibacterial activity.²⁶⁹

²⁶² P. E. Dupont, Ph. D. Thesis, Rensselaer Polytech. Inst., New York, 1968; *Diss. Abstr.* **29**, 4092 (1969); *Chem. Abstr.* **71**, 112147 (1969).

²⁶³ T. Sheradsky and A. Elgavi, *Isr. J. Chem.* **6**, 895 (1968).

²⁶⁴ A. Mooradian and P. E. Dupont, *Tetrahedron Lett.*, 2867 (1967).

²⁶⁵ A. Mooradian, *Tetrahedron Lett.*, 407 (1967).

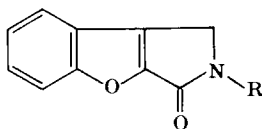
²⁶⁶ D. Kaminsky, J. Shavel, and R. I. Meltzer, *Tetrahedron Lett.*, 859 (1967).

²⁶⁷ T. Sheradsky, *J. Heterocycl. Chem.* **4**, 413 (1967).

²⁶⁸ A. Mooradian and P. E. Dupont, *J. Heterocycl. Chem.* **4**, 441 (1967).

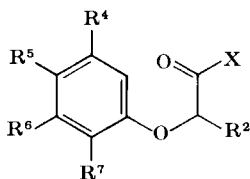
²⁶⁹ A. Mooradian, U.S. Patent 3,481,944 (1969); *Chem. Abstr.* **72**, 55237 (1970).

Complex benzofurans, such as N-substituted 3-oxo-1,3-dihydrobenzofuro[2,3-*c*]pyrroles (95),²⁶³ or bacteriostatic substituted 5,6,7,8-tetrahydrobenzofuro[2,3-*b*]pyridines,²⁷⁰ 4a-alkoxy-1,2,3,4,4a,9b-hexahydrobenzofuro[3,2-*c*]pyridines and polysubstituted benzofuro[3,2-*c*]pyridines,²⁷¹ and other polyheterocyclic compounds with sulfur or nitrogen atoms^{272,273} have also been synthesized by this method.

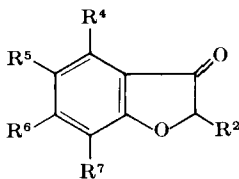


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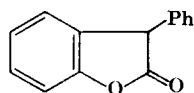
h. *Ring Closure of Aryloxyacetic Acids.* Acids with the general formula 96 ($X=OH$) undergo ring closure with the usual reagents (H_2SO_4 , P_2O_5 , PPA, etc.) giving 3(2*H*)-benzofuranones (97), usually in low yields.²⁷⁴ 2,3,5-Trimethylphenoxyacetic acid (96, $R^4=R^6=R^7=Me$) exceptionally gives 73% of 4,6,7-trimethyl-3(2*H*)benzofuranone (97) ($R^4=R^6=R^7=Me$, $R^2=H$) (with H_2SO_4).²⁷⁵ Acid chlorides (96, $X=Cl$) give the same result by intramolecular Friedel-Crafts reaction.^{208,276}



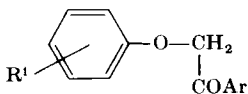
(96)



(97)



(98)



(99)

²⁷⁰ A. Mooradian (Sterling Drug Inc.), U.S. Patent 3,452,033 (1969), *Chem. Abstr.* **71**, 91284 (1969).

²⁷¹ C. J. Cattanch and R. C. Rees, *J. Chem. Soc. C*, 53 (1971).

²⁷² L. M. Sharkova, L. A. Aksanova, N. F. Kucherova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 762 (1971).

²⁷³ A. Aksanova, L. M. Sharkova, N. F. Kucherova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 1581, (1970); *Chem. Abstr.* **74**, 53589 (1971).

²⁷⁴ J. N. Chatterjea, S. N. P. Gupta, and V. N. Mehrota, *J. Indian Chem.* **42**, 205 (1965).

²⁷⁵ L. I. Smith and R. R. Holmes, *J. Amer. Chem. Soc.* **73**, 4296 (1951).

²⁷⁶ J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 981 (1964).

Cyclization of some α,α -disubstituted acids has recently been investigated: thus, 4,6-dimethoxy-2,2-dimethyl-3(2*H*)-benzofuranone is obtained in 47% yield from 2-(3,5-dimethoxyphenoxy)-2-methylpropionic acid.²⁷⁷

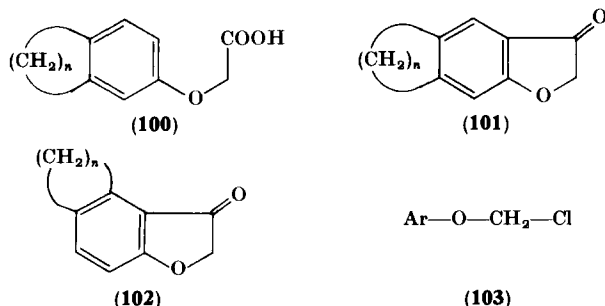
Rearrangements have been observed in the case of aryloxyacetic acids α -substituted by an aryl group (**96**, $R^1 = H$, $R^2 = Ph$, $X = OH$), which give 3-phenyl-2(3*H*)-benzofuranone (**98**).²⁷⁸ 2,4-Dichlorophenoxyacetic acid and its chloride do not undergo ring closure by any method.²⁷⁹

Ring closure of the acid chlorides (**96**, $X = Cl$) gives varying results according to their nature and that of the solvent.

In a substituted aromatic solvent (e.g., *m*-xylene), the acid chlorides (**96**, $X = Cl$) exclusively give the intermolecular Friedel-Crafts reaction, leading to ketones (**99**, $Ar = m$ -xylyl).²⁴⁰

In benzene and in the presence of $AlCl_3$, phenoxyacetyl chlorides (whether ring-substituted or not) give miscellaneous products according to the nature of the substituent, due to intermolecular and intramolecular reactions. Parallel decarbonylation is also observed, followed by alkylation of the solvent and rearrangement of the resulting benzyl ether to a substituted phenol and a diphenylmethane, or to a benzylphenol.^{280,281} In spite of this, significant yields of monosubstituted, 4,5-disubstituted, and 5,6-disubstituted benzofuranones (**97**) are formed when the reaction is effected at 5°. ²⁸² Ring closure of the chlorides of the bicyclic acids (**100**) gives a mixture of the benzofuranones **101** and **102**.^{282,283}

In carbon disulfide, aryloxyacetyl chlorides (except for thymoxyacetyl



²⁷⁷ C. P. Lo and R. L. Orsago, *J. Org. Chem.* **26**, 4758 (1961).

²⁷⁸ M. C. Khosla and N. Anand, *J. Indian Chem. Soc.* **3**, 232 (1965).

²⁷⁹ W. L. F. Armarego, *Aust. J. Chem.* **13**, 95 (1960).

²⁸⁰ M. H. Palmer and G. J. McVie, *J. Chem. Soc. B*, 742 (1968).

²⁸¹ M. H. Palmer and G. J. McVie, *J. Chem. Soc. B*, 745 (1968).

²⁸² M. H. Palmer and N. M. Scollick, *J. Chem. Soc. C*, 2833 (1968).

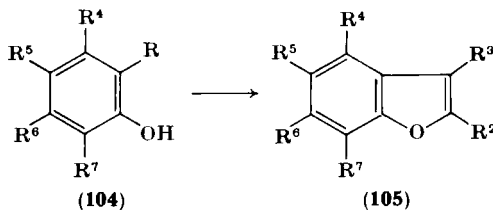
²⁸³ M. H. Palmer and N. M. Scollick, *J. Chem. Soc. C*, 2836 (1968).

chloride²⁰⁸) and aluminium chloride give, by decarbonylation, aryl chloromethyl ethers (**103**).²⁸⁴ The ready conversion of benzofuranones (**97**) into the corresponding benzofurans is surveyed in Section IV,D.

3. Ring Closure of Ortho-Substituted Phenols (Group 2)

These methods utilize molecules of type B (p. 362) (\equiv **104**)

a. *Synthesis of Benzofurans by Thermal Ring Closure and Cyclo-dehydrogenation (Thermal, Catalytic or Photochemical) of o-Substituted Phenols. The Hansch Reaction.* *o*-Alkylhydroxy-compounds on heating with a suitable catalyst give either a benzofuran or a 2,3-dihydrobenzofuran with the same number of carbon atoms.²⁸⁵⁻²⁹² Side products are formed by decomposition of the starting material. The initial phenol can be *o*-alkylated and ring-closed in one stage.



The unsaturated compound first formed from the *o*-alkylphenol then undergoes ring closure. Some phenoxyated alcohols, looked upon as forerunners of compounds (**104**), such as 1-phenoxy-2-propanol, also undergo ring closure with dehydrogenation (400°, Al₂O₃) to benzofuran derivatives, viz., to 2-methylbenzofuran (mixed with the 2,3-dihydro derivative).²⁹⁰

Numerous catalysts have been investigated: chromium catalysts²⁸⁶⁻²⁸⁹ on various substrates (used in the vapor phase and activated by traces of various compounds), copper carbon oxysulfide,²⁹³⁻²⁹⁵ catalysts based

²⁸⁴ M. H. Palmer and G. J. McVie, *Tetrahedron Lett.*, 6405 (1966).

²⁸⁵ R. Gaertner, *J. Amer. Chem. Soc.* **73**, 4400 (1951).

²⁸⁶ C. Hansch, W. Saltensall, and J. Sattle, *J. Amer. Chem. Soc.* **71**, 943 (1949).

²⁸⁷ C. Hansch, C. Scott, and H. Keller, *Ind. Eng. Chem.* **42**, 2114 (1950).

²⁸⁸ C. Hansch and G. Helmkamp, *J. Amer. Chem. Soc.* **73**, 3080 (1951).

²⁸⁹ B. B. Corson, H. E. Tiefenthal, P. E. Nichols, and W. Heintzelmann, *J. Amer. Chem. Soc.* **77**, 5428 (1955).

²⁹⁰ B. B. Corson, W. J. Heintzelmann, H. E. Tiefenthal, and P. E. Nichols, *J. Org. Chem.* **17**, 971 (1952).

²⁹¹ N. I. Shuikin, E. A. Viktorova, S. Li, and E. A. Karakhanov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.*, 2054 (1961); *Chem. Abstr.* **57**, 8478 (1962).

²⁹² G. E. Illingworth and J. J. Louvar, U.S. Patent 3,285,932 (1966); *Chem. Abstr.* **66**, 28649 (1967).

on LiOH and H_2PtCl_6 at 550° .²⁹² Without a catalyst, thermal ring closure of propylphenols and butylphenols, in the presence of steam at 700° – 750° , gives very low yields of benzofurans,²⁹⁶ but from *o*-allenyl phenol (**104**, $\text{R} = \text{CH}=\text{C}=\text{CH}_2$) excellent yields of 3-methylbenzofuran (**105**, $\text{R}^3 = \text{Me}$) are obtained.²⁸⁵

The method has been extended to the indole series.²⁸⁸

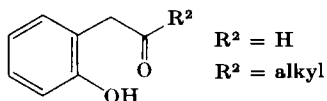
The industrial synthesis of benzofuran has been investigated.

i. *From phenol and acetylene*.^{297–299} Synthesis was on an alumina-based catalyst at 640° (various impurities have been detected: β -naphthol, naphthalene, dibenzofuran and fused-ring aromatic hydrocarbons, such as chrysene).

ii. *From phenol and ethanol*. Chromic acid catalyst with iron oxide is used as promoter.³⁰⁰ 2-Allylphenols can also undergo photochemical (UV) ring closure: this gives exclusively 2,3-dihydrobenzofuran and chroman derivatives.³⁰¹ The same derivatives are formed under certain conditions (heating under pressure in the presence of metal phenates) from phenol and conjugated dienes.³⁰²

Finally, condensation of phenols with various aliphatic compounds in the presence of a catalyst or a dehydrating compound, such as KHSO_4 , H_3PO_4 , PPA, leads to 2,3-dihydrobenzofuran derivatives. It has been the subject of many investigations^{303–309} in the field of chemical technology.

b. *Synthesis of Benzofuran Derivatives by Cyclodehydration of o-Hydroxyaryllactaldehydes and o-Hydroxybenzyl Alkyl Ketones*. The starting material has the general formula (type B, p. 362).



²⁸³ D. E. Boswell, P. S. Landis, E. N. Givens, and P. E. Venuto, *Ind. Eng. Chem., Proc. Res. Develop.* **7**, 215 (1968); *Chem. Abstr.* **69**, 96365 (1968).

^{294a} D. E. Boswell and P. S. Landis, *Bull. New Jersey Acad. Sci.*, **11**, 71 (1966).

^{294b} P. S. Landis and D. E. Boswell (Mobil Oil Corp.), U.S. Patent 3,420,854 (1969); *Chem. Abstr.* **70**, 68122 (1969).

²⁹⁵ E. N. Givens and P. B. Venuto, *J. Catal.* **15**, 318 (1969).

²⁹⁶ K. T. Raudsepp and H. E. Raudsepp, *Eesti NSV Tead. Akad. Toim. Keem. Geol.* **20**, 3 (1971); *Chem. Abstr.* **74**, 87531 (1971).

²⁹⁷ B. Sila and T. Lesiak, *Rocz. Chem.* **35**, 1519 (1961).

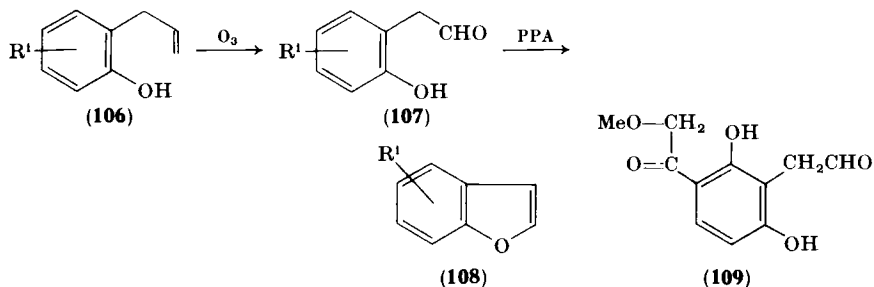
²⁹⁸ T. Lesiak, *Rocz. Chem.* **36**, 1533 (1962).

²⁹⁹ B. Sila, T. Lesiak, W. Zacharewicz, K. Waselewski, and B. Uszewski, *Prymysl. Chem.* **11**, 70 (1962).

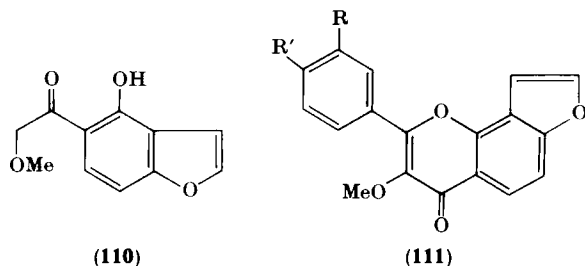
³⁰⁰ A. Krauze, *Rocz. Chem.* **37**, 827 (1963).

³⁰¹ W. Frater, and H. Schmid, *Helv. Chim. Acta* **50**, 255 (1967).

i. From *o*-hydroxyarylacetaldehydes ($R^2 = H$). This general method provides, from a simple or fused *o*-allylphenol (**106**) (obtained by Claisen rearrangement of the allyloxy derivative), the corresponding simple or fused benzofuran (**108**), unsubstituted on the furan ring.

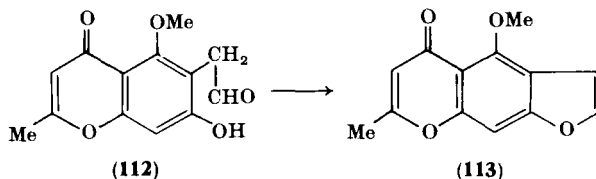


Ozone or performic acid readily converts **106** into the aldehyde **107**, which then undergoes cyclodehydration to **108** with PPA.²⁰¹ Thus, 4-allyloxy-2-hydroxy- ω -methoxyacetophenone gives (Claisen) 3-allyl-2,4-dihydroxy- ω -methoxyacetophenone, then (with ozone) aldehyde (**109**) and 4-hydroxy-5(methoxyacetyl)benzofuran (**110**).



- ³⁰² Farbenfabriken Bayer AG, British Patent 906,483 (1962); *Chem. Abstr.* **58**, 6806 (1963).
³⁰³ I. P. Losev, O. V. Smirnova, and L. P. Ryadneva, *Sb. Stat. Obshch. Khim. Akad. Nauk SSSR* **1**, 548 (1953); *Chem. Abstr.* **49**, 832 (1955).
³⁰⁴ N. I. Shuikin, E. A. Viktorova, and I. E. Pokrovskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1094 (1961); *Chem. Abstr.* **55**, 27259 (1961).
³⁰⁵ N. I. Shuikin, E. A. Viktorova, I. E. Pokrovskaya, and T. G. Malysheva, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1660 (1961); *Chem. Abstr.* **56**, 4651 (1962).
³⁰⁶ E. A. Viktorova, N. I. Shuikin, and B. G. Bubnova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1657 (1961); *Chem. Abstr.* **56**, 8610 (1962).
³⁰⁷ A. I. Kakhniashvili and G. S. Glonti, *Zh. Org. Khim.* **2**, 327 (1966); *Chem. Abstr.* **65**, 2155 (1967).
³⁰⁸ A. I. Kakhniashvili, G. S. Glonti, B. D. Bagratishvili, M. L. Kantariya, and D. S. Ioramsh, *Soobsch. Akad. Nauk Gruz. SSR* **36**, 323 (1964); *Chem. Abstr.* **63**, 4214 (1965).
³⁰⁹ E. A. Viktorova and N. N. Tsitsugina, *Vestn. Moskv. Univ. Khim.* **11**, 450 (1970); *Chem. Abstr.* **73**, 130722 (1970).

This method is suited to the synthesis of natural benzofuran derivatives: karanjin (**111**, $R = R' = H$) (a furoflavone) and pongapin (**111**, $RR' = O-CH_2-O$) have been prepared in this way,²⁰¹ as well as khellin (**26**).³¹⁵ From the chromone acetaldehyde (**112**), visnagin (**113**) (4-methoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one) was synthesized.³¹⁰



The treatment of the allyl derivative with ozone has been advantageously replaced by the osmium tetroxide- KIO_4 method: psoralene has thus been made from a 7-acetoxy-6-alkylcoumarin^{311,312,315} and xanthotoxin,^{311,312} angelicin (**28**),³¹¹ and dehydrodemethoxyelliptone (**114**)³¹³ ([1]benzopyrano[3,4-*b*]furo[2,3-*h*][1]benzopyran-6-one), the furoflavones and furoisoflavones,³¹⁴ khellin (**26**),³¹⁵ the angular furoxanthone (**115**),³¹⁶ and bergaptene³¹⁷ (4-methoxypsoralene) have all been synthesized.

The synthesis of the (\pm) 4-hydroxy-6-methoxytetrahydrofuro[2,3-*b*]-benzofuran ring (**116**), a degradation product of natural substances of the sterigmatocystin series, is similar,³¹⁸ as is the synthesis of the dihydro derivative (**117**) from the *o*-acetylated acetaldehyde (**118**), a nonisolated intermediate which is ring-closed to **119** and then heated in toluene to give **117**. The last is the starting point for the synthesis of aflatoxin M_1 (**49**).¹⁵³

Cyclizations of *o*-hydroxyarylacetaldehydes and of epoxides proceed by similar mechanisms, so we include in this section the synthesis of the

³¹⁰ R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron* **3**, 230 (1958).

³¹¹ T. R. Seshadri and M. S. Sood, *Indian J. Chem.* **1**, 291 (1963).

³¹² N. J. De Souza, P. V. Nayak, and E. Secco, *J. Heterocycl. Chem.* **3**, 42 (1966).

³¹³ K. S. Raizada, P. S. Sarin, and T. R. Seshadri, *J. Sci. Ind. Res., Sect. B* **19**, 76, (1960); *Chem. Abstr.* **55**, 22303 (1961).

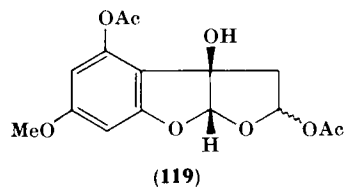
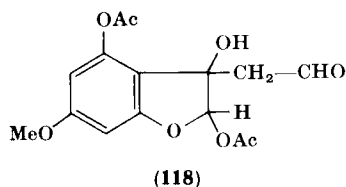
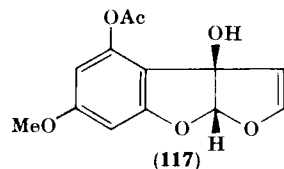
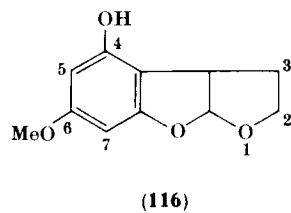
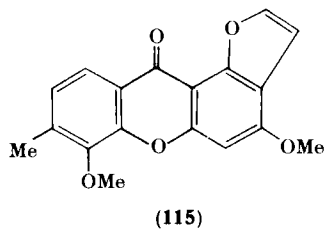
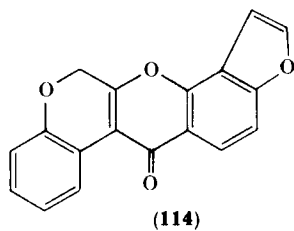
³¹⁴ R. N. Khanna and T. R. Seshadri, *Indian J. Chem.* **1**, 385 (1963); *Chem. Abstr.* **60**, 1724 (1964).

³¹⁵ R. Aneja, S. K. Mukerjee, and T. R. Seshadri, *Chem. Ber.* **93**, 297 (1960).

³¹⁶ E. D. Burling, A. Jefferson, and F. Scheinmann, *Tetrahedron Lett.*, 599 (1964).

³¹⁷ V. K. Ahluwalia, T. R. Seshadri, and P. Venkateswarlu, *Indian J. Chem.* **7**, 831 (1969); *Chem. Abstr.* **71**, 112948 (1969).

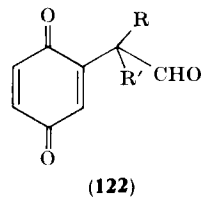
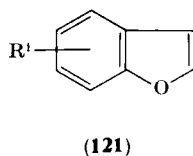
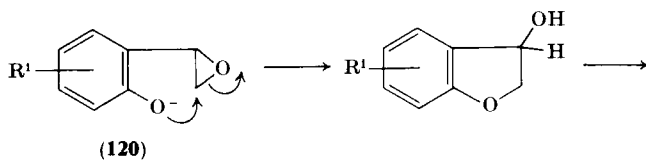
³¹⁸ J. A. Knight, J. C. Roberts, and P. Roffey, *J. Chem. Soc. C*, 1308 (1966).



Δ toluene

benzofuran ring from *o*-hydroxylated aldehydes and dimethyloxosulfonium methylide, which has recently been described;^{319,320} it leads to 3-hydroxy-2,3-dihydrobenzofurans, then to benzofurans (121), through the epoxides (120).

Opinions differ regarding the extension of the method to enolizable



³¹⁹ B. Holt and P. A. Lowe, *Tetrahedron Lett.*, 683 (1966).

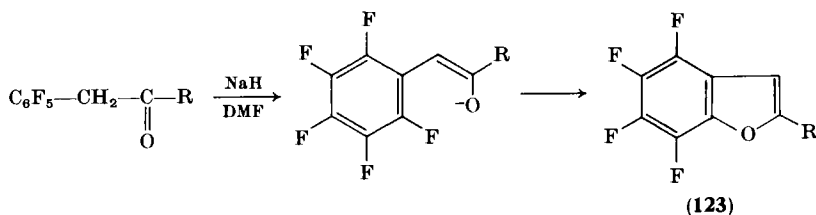
³²⁰ M. Darnault, G. Fontaine, and P. Maitte, *C. R. Acad. Sci., Ser. C* **266**, 1712 (1968).

carbonyl compounds: *o*-hydroxyacetophenone is described by some³¹⁹ as giving 3-methylbenzofuran with 80% yield, by others³²⁰ as resisting all attempts at ring closure.

A similar method, which involves the formation of the epoxide through reaction of diazomethane on 1-formyl-2-hydroxyxanthone, leads directly to 11*H*-furo[2,3-*a*]xanthen-11-one.³²¹

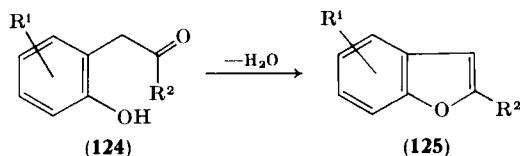
Photocyclization in benzene of *p*-quinones with an acetaldehyde group, such as 2-(1,4-benzoquinonyl)-2-methylpropionaldehyde, gives 5-hydroxy-3-methylbenzofuran, 3,3-dimethyl-5-hydroxy-2(3*H*)-benzofuranone and the cyclic hemiacetal of 2-(2,5-dihydroxyphenyl)-2-methylpropionaldehyde.³²²

Polyfluorophenylacetaldehydes show a novel nucleophilic ring closure reaction: pentafluorophenylacetaldehyde, treated with sodium hydride in DMF, gives 4,5,6,7-tetrafluorobenzofuran (**123**, R = H) (13% yield). Under the same conditions, 2-pentafluorophenylacetophenone gives the 2-phenyl derivative (**123**, R = Ph) (76% yield).³²³



ii. From *o*-hydroxybenzyl alkyl ketones (R^2 = alkyl). *o*-Hydroxyphenylacetone (**124**, R^2 = Me, R^1 = H) very readily undergoes ring closure, almost spontaneously,³²⁴ under the influence of acidic reagents (hydrochloric acid in ethanol), to 2-methylbenzofuran (**125**, R^2 = Me).²⁰¹ Other substituted derivatives react analogously.³²⁴

The same type of reaction has recently been observed on the products of the alkaline degradation of 3-acyl-2-alkylbenzofurans (**126**), which



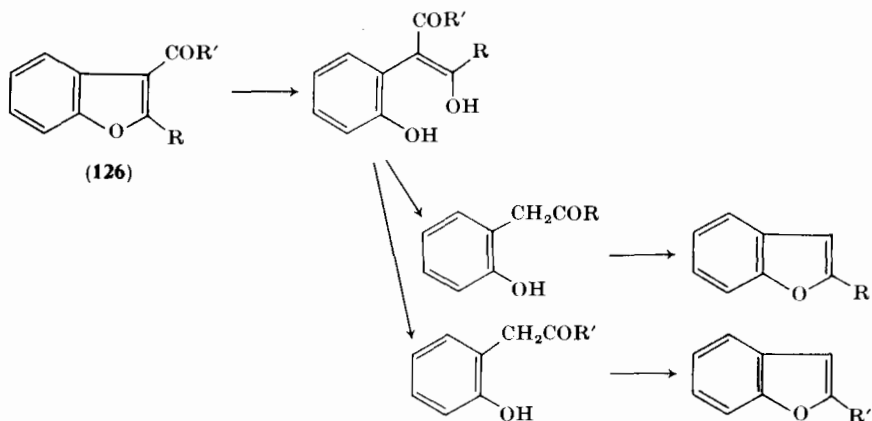
³²¹ F. Lamb and H. Suschitzky, *Tetrahedron* **5**, 1 (1959).

³²² J. M. Bruce and D. Creed, *J. Chem. Soc. C*, 649 (1970).

³²³ G. M. Brooke, W. K. R. Musgrave, and T. R. Thomas, *J. Chem. Soc. C*, 3596 (1971).

³²⁴ S. W. Tinsley, *J. Org. Chem.* **24**, 1197 (1959).

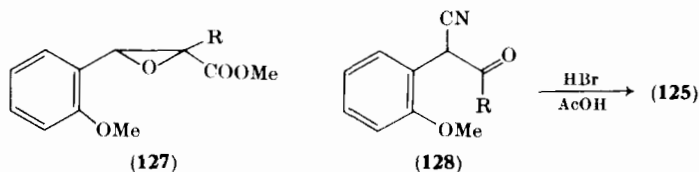
undergo rearrangement to 2-alkylbenzofurans via intermediate *o*-hydroxybenzyl alkyl ketones: the latter undergo spontaneous ring closure in acidic media.³²⁵



The methoxy derivatives may be treated directly: *o*-methoxyphenylacetone, heated with hydrobromic acid in acetic acid, gives 2-methylbenzofuran.³²⁶ *o*-Methoxylated phenylacetones are readily prepared by glycidic synthesis from *o*-methoxylated aromatic aldehydes: the intermediate glycidic ester (127) can be directly converted by pyridine hydrochloride into a 2-alkylbenzofuran in 40–80% yield.¹⁰⁵

Ring closure of α -cyano-*o*-methoxyphenylacetones (128), prepared by condensing a 2-methoxyphenylacetone with an ester (R-COOEt), is readily achieved (HBr/AcOH).^{327,328} The cyano group is hydrolyzed off, during the cyclization.

This reaction succeeds with R = benzyl,³²⁷ 2-, 3-, and 4-pyridyl, and 2-quinolyl.³²⁹



³²⁵ R. Royer and E. Bisagni, *Bull. Soc. Chim. Fr.*, 395 (1960).

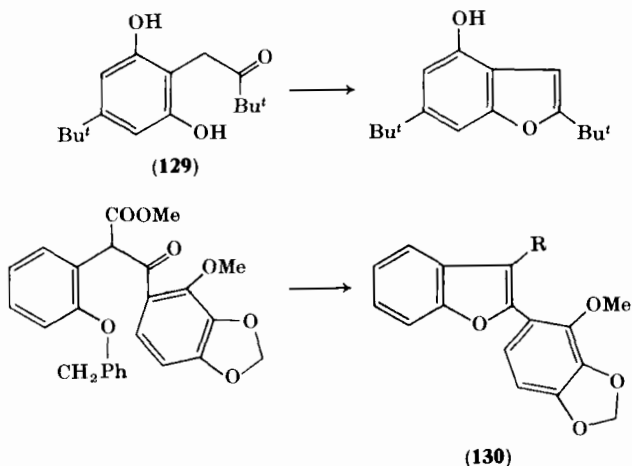
³²⁶ L. Christiaens and M. Renson, *Bull. Soc. Chim. Belges* **79**, 235 (1970).

³²⁷ J. N. Chatterjea, *Experientia* **12**, 371 (1956).

³²⁸ J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.* **34**, 98 (1957).

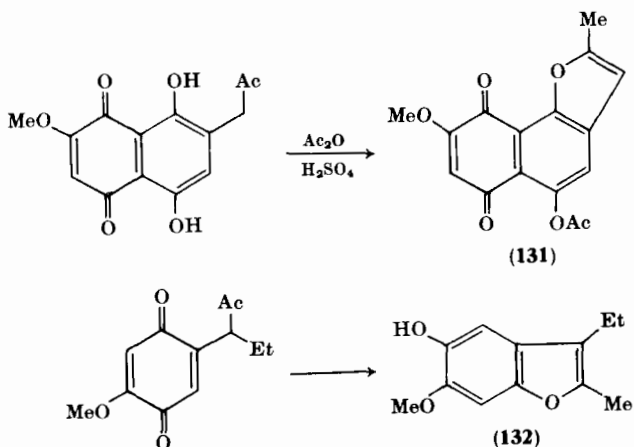
³²⁹ H. J. Ziegler, H. Inion, G. Aussems, A. Christiaens, F. Chaillet, and R. Charlier, *Chem. Ther.*, 159 (1971).

The formation of, e.g., 2,6-di-*t*-butyl-4-hydroxybenzofuran from **129**, is easily accomplished.³³⁰



Treatment of some substituted *o*-benzyloxy-ketones with hydrochloric acid in acetic acid gives, e.g., the carboxylic ester (**130**, R = COOMe), then the corresponding benzofuran (**130**, R = H) through debenzylation, ring closure, hydrolysis, and decarboxylation.³³¹

In the naphthofuran series, monoacetyl anhydronorjavanicin (**131**) has been synthesized from the *o*-hydroxyarylacetone norjavanicin.³³²



³³⁰ H. Alles, D. Dormann, and H. Musso, *Chem. Ber.* **103**, 2526 (1970).

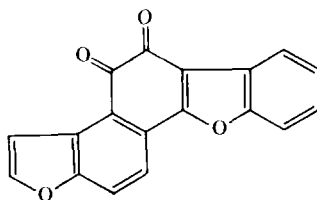
³³¹ A. F. Wagner, A. N. Wilson, and F. Folkers, *J. Amer. Chem. Soc.* **81**, 5441 (1959).

³³² W. S. Chilton, *J. Org. Chem.* **33**, 4299 (1968).

2-Acetyl *p*-quinones by reduction give 2-acetyl phenols, which undergo ring closure to the corresponding 2-methylbenzofurans; an instance is the synthesis of 2,4,6,7-tetramethylbenzofuran.³³³ Heterocyclic ring closure with α -substituted *o*-hydroxyphenylacetones seems easier:³³⁴ reduction of 2-(α -acetopropyl)-5-methoxybenzoquinone, in an acidic medium leads directly to the benzofuran (132).

An important extension of this method has made it possible to synthesize polycyclic benzofurans under the influence of various demethylating and dehydrating media.³³⁵ For such ring closures, pyridine hydrochloride is especially suitable: thus coumestan has been synthesized from 4-hydroxy-3-(2-methoxyphenyl)coumarin.⁸ 4,7-Dihydroxy-3-(2,4-dimethoxyphenyl)coumarin gives coumestol with aniline hydrochloride;³³⁶ other polymethoxycoumestans have been obtained with pyridine hydrochloride or with HBr (or HI) and acetic acid.³³⁷⁻³³⁹

Pterocarpan have been synthesized from suitable isoflavones (HCl, THF).^{340,341} Difuranic pentacyclic heterocycles, such as 133, have also been obtained through ring closure with pyridine hydrochloride, HI or AlCl_3 .³⁴²



(133)

³³³ R. Magnusson, *Acta Chem. Scand.* **18**, 421 (1964).

³³⁴ A. Muller, M. Meszaros, and K. Kormendy, *J. Org. Chem.* **19**, 472 (1954).

³³⁵ T. R. Govindachari, K. Nagarajan, and P. C. Parthasarathy, *J. Chem. Soc.*, 548 (1957).

³³⁶ O. H. Emerson, U.S. Patent 2,863,915 (1958); *Chem. Abstr.* **58**, 8079 (1959).

³³⁷ T. R. Govindachari, K. Nagarajan, and P. C. Parthasarathy, *Tetrahedron* **15**, 129 (1961).

³³⁸ N. R. Krishnaswamy, T. R. Seshadri, and B. R. Sharma, *Indian J. Chem.* **4**, 120 (1966).

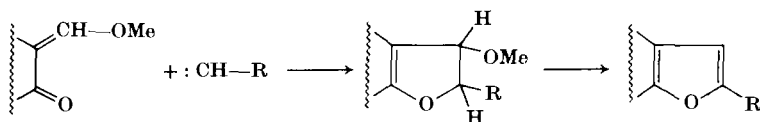
³³⁹ K. Fukui and M. Nakayama, *Nippon Kagaku Zasshi* **85**, 790 (1964); *Chem. Abstr.* **62**, 16179 (1965).

³⁴⁰ V. Kalra, A. S. Kukla, and T. R. Seshadri, *Tetrahedron* **23**, 3221 (1967).

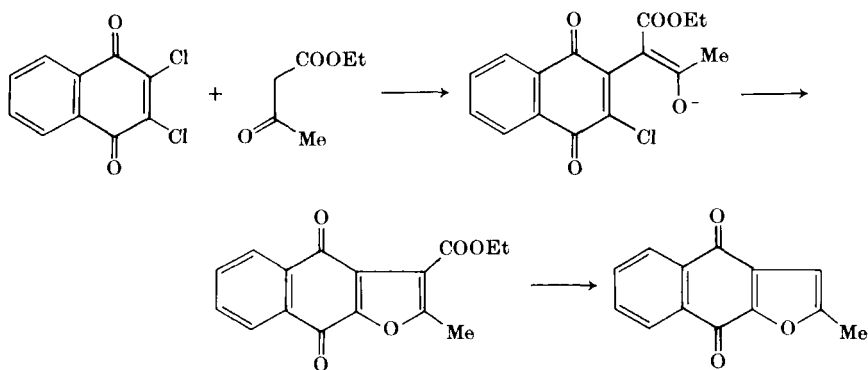
³⁴¹ V. Uchiyama, and M. Matsui, *Agr. Biol. Chem.* **31**, 1490 (1967); *Chem. Abstr.* **69**, 18974 (1968).

³⁴² Y. Kawase, M. Nanbu, and H. Yanagihara, *Bull. Chem. Soc. Jap.* **41**, 1201 (1968).

iii. *Subsidiary methods.* A general synthesis of the furan ring by formal 1,4 addition of carbethoxycarbene ($R = \text{COOEt}$) with α -methoxymethylene ketones is particularly suitable for preparing complex benzofuran derivatives.³⁴³



In some instances, the electrophilic ring closure reaction can be replaced by a nucleophilic reaction in an alkaline medium, such as used for polyfluorinated derivatives: the compound obtained by condensing 2,3-dichloro- α -naphthoquinone with ethyl acetoacetate thus undergoes ring closure³⁴⁴ (Scheme 1).



SCHEME 1

c. *Synthesis of Benzofuran Derivatives by Condensation of Quinones with β -Ketonic Compounds, Unsaturated Ethers and Esters, Enamines.* In this type of reaction, considerably developed since 1953, benzofuran or 2,3-dihydrobenzofuran derivatives are obtained by condensation of quinones with compounds with reactive methylene groups (β -diketones, β -keto esters, malononitrile, ethyl cyanoacetate) (the Pechmann reaction, 1888) or with vinyl ethers, unsaturated β -amino esters, or enamines.

i. *β -ketonic compounds.* In the presence of ZnCl_2 , *p*-benzoquinone condenses with acetylacetone (**134**, $R^2 = \text{Me}$, $R^3 = \text{Ac}$),^{345,346} ethyl

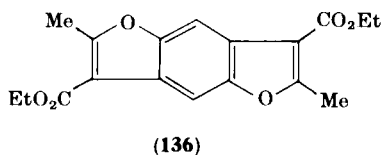
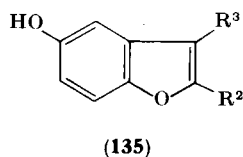
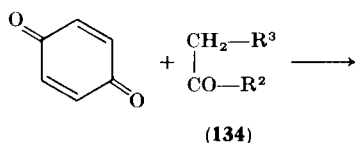
³⁴³ D. L. Storm and T. A. Spencer, *Tetrahedron Lett.*, 1865 (1967).

³⁴⁴ C. A. Reynolds, J. A. Van Allan, and R. E. Adel, *J. Org. Chem.* **30**, 3819 (1965).

³⁴⁵ E. Bernatek, *Acta Chem. Scand.* **6**, 160 (1952).

³⁴⁶ E. Bernatek, *Acta Chem. Scand.* **7**, 677 (1953).

acetoacetate (**134**, $R^2 = \text{Me}$, $R^3 = \text{COOEt}$),^{347,348} and ethyl butyrylacetate (**134**, $R^2 = \text{Pr}$, $R^3 = \text{COOEt}$),³⁴⁹ giving the corresponding substituted benzofurans (**135**) (Table II). The reaction occurs in acetone or in ethanol (in the latter solvent, a furobenzofuran derivative, **136**, has been detected in small amounts).^{347,361} The intermediate acetoacetic esters can be isolated when the reaction is catalyzed by an alkali metal alkoxide.³⁵⁵ Many investigations cover various β -ketonic compounds



³⁴⁷ E. Bernatek and T. Ledaal, *Acta Chem. Scand.* **12**, 2053 (1958).

³⁴⁸ A. N. Grinev, P. Bon-Khvar, and A. P. Terentyev, *Zh. Obshch. Khim.* **27**, 821, 1087, 1172 (1957).

³⁴⁹ W. Schoetensack, G. Hollmann, and H. Haegle, U.S. Patent 3,235,566 (1966); *Chem. Abstr.* **64**, 11176 (1966).

³⁵⁰ A. N. Grinev, A. Bukhtenko, and A. P. Terentyev, *Zh. Obshch. Khim.* **29**, 945 (1959); *Chem. Abstr.* **54**, 1481 (1960).

³⁵¹ A. N. Grinev and A. P. Terentyev, *Zh. Obshch. Khim.* **28**, 78 (1958).

³⁵² A. N. Grinev, N. K. Venetseva, and A. P. Terentyev, *Zh. Obshch. Khim.* **28**, 1856 (1958).

³⁵³ J. Green, D. McHale, S. Marcinkiewicz, P. Mamelis, and P. R. Watt, *J. Chem. Soc.*, 3362 (1959).

³⁵⁴ S. E. Fumagalli and C. Eugster, *Helv. Chim. Acta* **54**, 959 (1971).

³⁵⁵ R. Adams and C. Whitaker, *J. Amer. Chem. Soc.* **78**, 658 (1956).

³⁵⁶ A. N. Grinev, P. Bon-Khvar, V. N. Frosin, and A. P. Terentyev, *J. Gen. Chem. SSSR* **26**, 564 (1956).

³⁵⁷ A. N. Grinev, and A. P. Terentyev, *Vestn. Mosk. Univ., Ser. Mat. Mekh. Astron. Fis. Khim.* **12**, 147 (1957); *Chem. Abstr.* **53**, 3187 (1959).

³⁵⁸ A. N. Grinev, N. K. Venetseva, and A. P. Terentyev, *J. Gen. Chem. SSSR* **27**, 1174 (1957).

³⁵⁹ K. C. Brannock and R. D. Burpitt (Eastman Kodak Co.), U.S. Patent 3,285,937 (1966); *Chem. Abstr.* **66**, 37762 (1967).

³⁶⁰ P. Kuser, E. F. Frauenfelder, and C. Eugster, *Helv. Chim. Acta* **64**, 969 (1971).

³⁶¹ A. N. Grinev, N. K. Venetseva, and A. P. Terentyev, *Zh. Obshch. Khim.* **27**, 1090 (1957); *Chem. Abstr.* **52**, 3761 (1958).

TABLE II
CONDENSATION OF BENZOQUINONES WITH β -KETONIC COMPOUNDS
OR VINYL ETHERS

Benzoquinone	Ketonic compounds $R^2\text{---CO---CH}_2\text{---}R^3$	Benzofurans	Refer- ences
Unsubstituted	$R^2 = \text{Me}, R^3 = \text{Ac}$	2-Me 3-Ac 5-OH	345, 346
Unsubstituted	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2-Me 3-COOEt 5-OH	347, 348
Unsubstituted	$R^2 = \text{Bu}, R^3 = \text{COOEt}$	2-Pr 3-COOH 5-OH	349
Unsubstituted	$R^2 = 2\text{-furyl}, R^3 = \text{COOEt}$	2-(2-Furyl) 3-COOEt 5-OH	350
2-OMe	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2-Me 3-COOEt 5-OH 6-OMe	351
2-Me	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2,6-DiMe 3-COOEt 5-OH	351
2,3-DiCl	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2-Me 3-COOEt 5-OH 6,7-DiCl	352
2,5-DiMe—	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2,4,7-TriMe 3-COOEt 5-OH	353
2-Ac	$R^2 = \text{Me}, R^3 = \text{COOEt}$	2-Me 3-COOEt 4-Ac 5-OH	354
Various sub- stituted (R^1)	$R^2 = \text{Me}, R^3 = \text{CO---Ph}$	2-Ph 3-COOEt R^1	355–358
	Vinyl ethers R^2 $\begin{array}{c} \diagdown \\ \text{C}=\text{CH---OR}_1 \\ \diagup \\ R^3 \end{array}$	2,3-Dihydrobenzofurans	
Unsubstituted	$R^1 = \text{Et}, R^2 = R^3 = \text{Me}$	2-OEt 3,3-diMe 5-OH	359
2-Acetyl	$R^1 = \text{R}, R^2 = R^3 = \text{Me}$	2-OR 4-Ac 5-OH	360

and substituted *p*-quinones,³⁶² and unsubstituted^{362,363} or substituted naphthoquinones.³⁶⁴

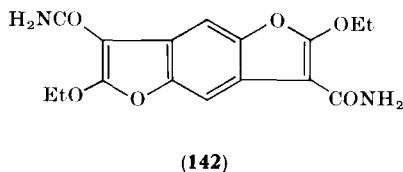
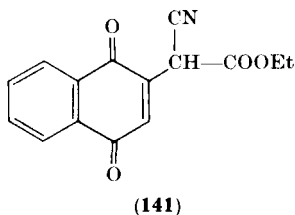
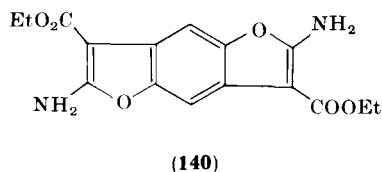
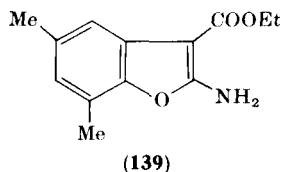
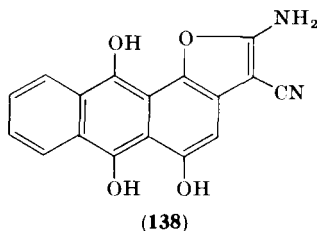
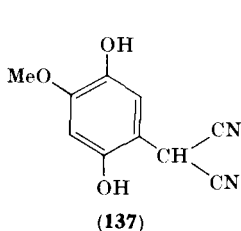
ii. *Malononitrile and ethyl cyanoacetate*. Similarly, 2-aminobenzofuran derivatives have been obtained with malononitrile: (138),³⁶⁵ and with ethyl cyanoacetate: (139) from 2,4-dimethyl ortho-quinol acetate,^{366–639} (140) from *p*-benzoquinone. From methoxy *p*-benzoquinone and

³⁶² S. Ebine, *Sci. Rep. Saitama Univ., Ser. A* **1**, 95 (1953); *Chem. Abstr.* **49**, 4619 (1955).

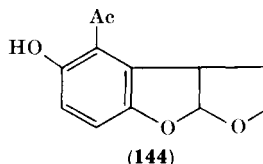
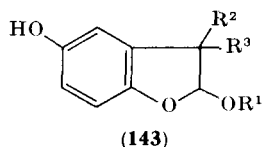
³⁶³ A. N. Grinev, V. N. Frosin, and A. P. Terentyev, *Zh. Obshch. Khim.* **31**, 1902 (1961).

³⁶⁴ A. N. Grinev, A. S. Mazentzev, and A. P. Terentyev, *Zh. Obshch. Khim.* **30**, 2306 (1960).

malononitrile,³⁷⁰ and from α -naphthoquinone³⁷¹ and ethylecyanoacetate, only the adducts, **137** and **141**, respectively, were isolated. With methoxy-*p*-benzoquinone, the reaction with ethyl cyanoacetate gives **142**.³⁷⁰



iii. *Vinyl ethers*. In the presence of BF_3 , the condensation of vinyl ethers with *p*-quinones forms 2,3-dihydrobenzofuran derivatives (**143**) with antioxidant and fungicidal properties.³⁵⁹



³⁶⁵ H. Junek, H. Sterk, and B. Hornischer, *Monatsh. Chem.* **99**, 2359 (1968).

³⁶⁶ F. Langer, F. Wessely, W. Specht, and P. Klezl, *Monatsh. Chem.* **89**, 239 (1958).

³⁶⁷ J. Derkosch and W. Specht, *Monatsh. Chem.* **92**, 542 (1961).

³⁶⁸ G. Spiteller, *Monatsh. Chem.* **92**, 1142 (1961).

³⁶⁹ A. R. Katritzky and J. Derkosch, *Monatsh. Chem.* **93**, 541 (1962).

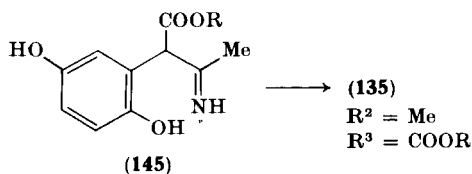
³⁷⁰ J. A. D. Jeffreys, *J. Chem. Soc.*, 2153 (1959).

³⁷¹ T. J. King and C. E. Newall, *J. Chem. Soc.*, 974 (1965).

2,3-Dihydrofuran (used as the vinyl ether), condenses with 2-acetyl-1,4-benzoquinone to give tetrahydrofuro[2,3-*b*]benzofuran (**144**), which is found in natural benzofuranoid xanthenes (sterigmatocystin).³⁷²

Quinones with electron-withdrawing groups (Ac, COOMe)^{354,360} react under mild conditions. With ethoxyacetylene, 4-acetyl-2-alkoxy-5-hydroxybenzofurans are obtained.³⁶⁰

iv. *β*-Aminocrotonic esters. The condensation of quinones with *β*-amino unsaturated esters (Nenitzescu reaction)³⁷³ has frequently been used for the synthesis of 5-hydroxylated indole derivatives. In many instances, the simultaneous formation of benzofuran derivatives has been observed from *β*-aminocrotonic esters, whether substituted³⁷⁴⁻³⁷⁶ or unsubstituted^{220,373,374,377} on the nitrogen atom. The supposed intermediate (**145**) (in the condensation of *p*-benzoquinone with a *β*-aminocrotonic ester) would give the benzofuran structure after cyclization of the phenolic oxygen to the imine (loss of ammonia).^{220,373-375,377}



The benzofuran ring has been obtained from *p*-benzoquinones with monosubstituted acetylenes (Li in liquid NH₃)³⁷⁸ and with *β*-diethylaminovinyl ketones.³⁷⁹⁻³⁸¹

v. *Enamines*. Reactions of the enamines from condensation of piperidine or morpholine with an aldehyde with *p*-benzoquinone gives 2,3-dihydro-5-hydroxy-2-piperidino(or morpholino)benzofurans (**146**),

³⁷² C. Eugster and P. Kuser, *Chimia* **18**, 358 (1964).

³⁷³ S. A. Monti, *J. Org. Chem.* **31**, 2669 (1966).

³⁷⁴ A. N. Grinev, G. Y. Uretskaya, and S. F. Tiberman, *Khim. Geterotsikl. Soedin.* **7**, 335 (1971).

³⁷⁵ A. N. Grinev, V. N. Ermakova, and A. P. Terentyev, *Zh. Obshch. Khim.* **32**, 1948 (1962); *Chem. Abstr.* **58**, 4498 (1963).

³⁷⁶ G. Domschke, *J. Prakt. Chem.* **32**, 140 (1966).

³⁷⁷ D. Raileanu and C. D. Nenitzescu, *Rev. Roum. Chim.* **10**, 339 (1965); *Chem. Abstr.* **63**, 9903 (1965).

³⁷⁸ W. Reid and A. Urschel, *Chem. Ber.* **91**, 2459 (1958).

³⁷⁹ F. A. Trofimov, T. I. Mukhanova, N. G. Tsyshova, A. N. Grinev, and K. S. Shadurskii, *Khim. Farm. Zh.* **1**, 14 (1967); *Chem. Abstr.* **69**, 2769 (1968).

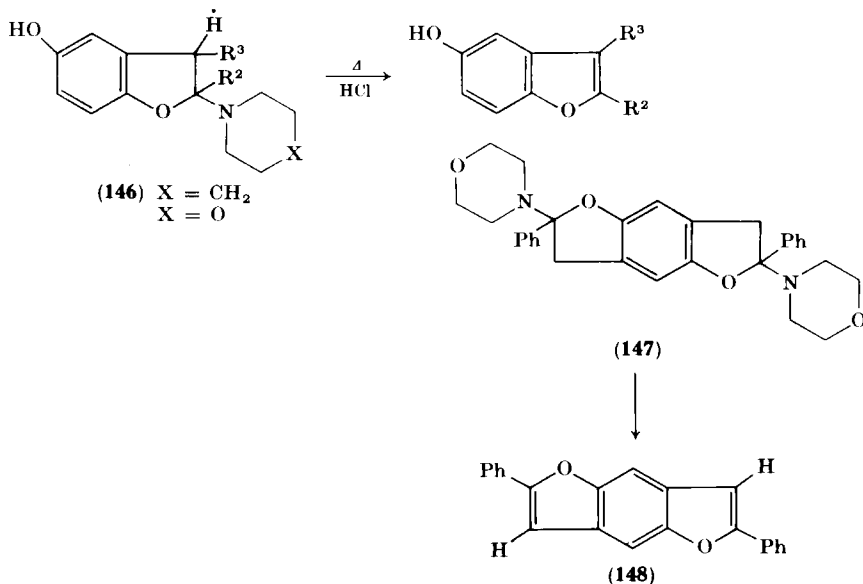
³⁸⁰ F. A. Trofimov, T. I. Mukhanova, A. N. Grinev, and V. I. Shvedov, *Zh. Org. Khim.* **3**, 2185 (1967).

³⁸¹ E. P. Fokin and E. P. Prudchenko, *Zh. Org. Khim.* **6**, 1251 (1970).

³⁸²⁻³⁸⁵ which can be converted into the corresponding 5-hydroxybenzofurans.³⁸⁶ N-Substituted enamines of 1,2,4 tricarbonyl compounds form a benzofuran as a by-product; the main product is the corresponding furo[2,3-*f*]benzofuran.³⁸⁷ 1-Morpholino-1-cyclohexene and *p*-benzoquinone give 1-morpholino-6-(2,5-dihydroxyphenyl)-1-cyclohexene, which, treated with HCl, gives 6,7,8,9-tetrahydrodibenzofuran.³⁸⁸

No benzofurans are obtained from substituted *p*-benzoquinones.³⁸⁹ The enamines of α -formyl ketones (AcOH, room temperature) with *p*-benzoquinone give 3-acyl-5-hydroxybenzofurans.³⁹⁰

N-(1-Phenylvinyl)morpholine and *p*-benzoquinone form **147** (R = Ph, R' = H), which gives **148** by double elimination of morpholine.³⁹¹ Diethyl aminofumarate and dimethyl aminomaleate give



³⁸² Upjohn Co., Netherlands Appl. 6,512,311 (1966); *Chem. Abstr.* **65**, 7142 (1966).

³⁸³ L. L. Skaletzky (Upjohn Co.), U.S. Patent 3,496,181 (1970); *Chem. Abstr.* **72**, 100754 (1970).

³⁸⁴ L. L. Skaletzky (Upjohn Co.), U.S. Patent 3,317,527 (1967); *Chem. Abstr.* **68**, 21826 (1968).

³⁸⁵ Upjohn Co., Netherlands Appl. 6,511,270 (1966); *Chem. Abstr.* **65**, 2230 (1966).

³⁸⁶ G. Domschke, *J. Prakt. Chem.* **32**, 144 (1966).

³⁸⁷ G. Domschke and H. Oelmann, *J. Prakt. Chem.* **311**, 786 (1969).

³⁸⁸ S. I. Zav'yalov, G. V. Kondratyeva and V. I. Gunar, *Izv. Akad. Nauk. SSSR, Ser. Khim.* **11**, 2086 (1964); *Chem. Abstr.* **62**, 7714 (1965).

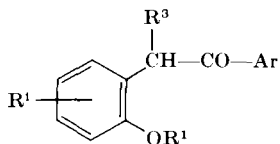
³⁸⁹ R. G. Allen, *J. Org. Chem.* **33**, 3346 (1968).

³⁹⁰ F. A. Trofimov, T. I. Mukhanova, K. S. Shadurskii, A. N. Grinev, and V. I. Shvedov, USSR Patent 194,103 (1967); *Chem. Abstr.* **69**, 2857 (1968).

³⁹¹ G. Domschke, *Chem. Ber.* **99**, 930 (1966).

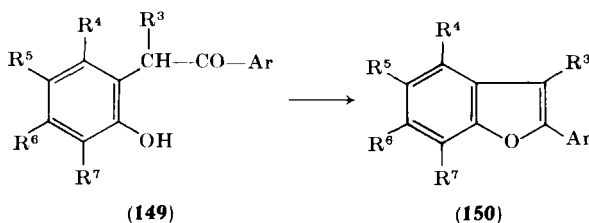
furo[2,3-*f*]benzofurans with *p*-benzoquinone (BF₃).³⁹² With alkylidene triphenylphosphoranes, *p*-quinones give *trans*-2,3-diphenyl-2,3-dihydrofuran derivatives.³⁹³

d. *Synthesis of Benzofuran Derivatives by Cyclodehydration of o-Hydroxydeoxybenzoins*. The starting molecule is of the type

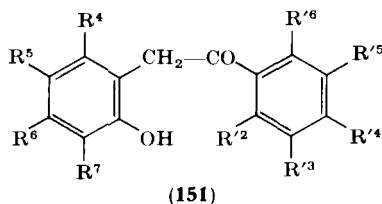


with R¹ = H or R¹ = Me.

i. R¹ = R³ = H (*α*-Unsubstituted *o*-hydroxy and -methoxy-deoxybenzoins). *o*-Hydroxydeoxybenzoins of general formula **149** give 2-arylbenzofurans in an acid-catalyzed (HCl, ethanol) cyclization (cf. Section IV, A, 3, b) (Table III). The reaction is fairly general³⁹⁷ although no rule



can be given; it is definitely influenced by substituents, as shown by the behavior of compounds **151** when distilled or sublimed: compounds



³⁹² G. Domschke and H. Oelmann, *J. Prakt. Chem.* **311**, 800 (1969).

³⁹³ H. J. Bestmann and H. J. Lang, *Tetrahedron Lett.*, 2101 (1969).

³⁹⁴ A. Spetz, *Acta Chem. Scand.* **10**, 1422 (1956).

³⁹⁵ W. Schulenberg and S. Archer, *J. Amer. Chem. Soc.* **82**, 2036 (1960).

³⁹⁶ H. Sugimoto, *Bull. Chem. Soc. Jap.* **39**, 1529 (1966); *Chem. Abstr.* **65**, 15311, (1966).

³⁹⁷ S. A. N. N. Bokhari and W. B. Whalley, *J. Chem. Soc.*, 5322 (1963).

³⁹⁸ W. J. Bowyer, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 542 (1957).

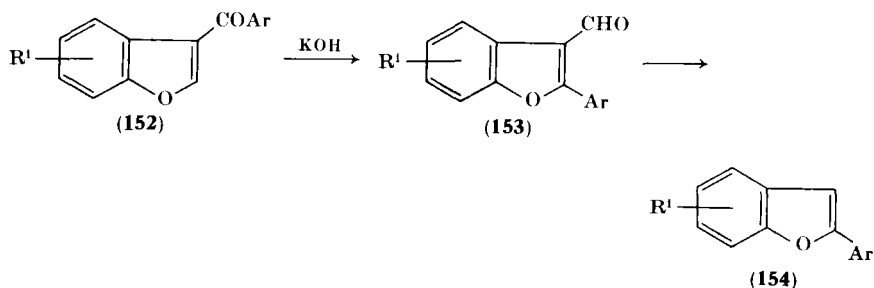
³⁹⁹ R. Royer, E. Bisagni and C. Hudry, *Bull. Soc. Chim. Fr.*, 933 (1961).

TABLE III
BENZOFURANS (150) FORMED BY RING CLOSURE OF
o-HYDROXYDEOXYBENZOINS AND *o*-METHOXYDEOXYBENZOINS

Benzofurans (150)	References
2-Ph	394, 395
2- <i>o</i> -C ₆ H ₄ OH	396
2-Ph 4,6-diOMe	398
2- <i>p</i> -C ₆ H ₄ OMe 4,6-diOMe	397
2-(2-OH-4,6-diOMe-C ₆ H ₂) 5,6-diOMe	398
2-(2-OH-3,4-diOMe-C ₆ H ₂) 4,6-diOMe	397
2- <i>p</i> -C ₆ H ₄ OH 6-COOH } 2- <i>p</i> -C ₆ H ₄ OMe 6-COOH }	399
2- <i>p</i> -C ₆ H ₄ OH 5-Me	400
2-(2-OH-5-Me-C ₆ H ₃) 5-Me	400
2-(2-OH-5-Me-C ₆ H ₃) 4,6-diMe	400
2-Ph	325
2-(2-OH-5-alkyl-C ₆ H ₃) 5-alkyl (R' = R ⁵ = H)	401

151 can be stable (R⁴=R⁶=OMe, R'¹=H)³⁹⁷ (R¹=H, R'⁴=OMe, R'²=OH),⁴⁰² or ring-close spontaneously (R⁴=R⁶=R'³=R'⁴=OMe, R'²=OH)³⁹⁷ or when distilled with (R⁴=R⁶=OMe, R'¹=H),³⁹⁷ or without (R⁴=R⁶=R'⁴=OMe, R'²=H³⁹⁷ or R'²=OH)³⁹⁸ dehydrating media.

A main synthesis of *o*-hydroxydeoxybenzoins is the alkaline degradation (KOH-ethanol) of 3-arylbzofurans (**152**); the latter can thus be converted into 2-arylbzofurans. The intermediate 3-formyl derivative (**153**) can be isolated (KOH-ethanol at room temperature, 22–24 hours) and is quickly converted into **154**, with formation of H-COOH, by



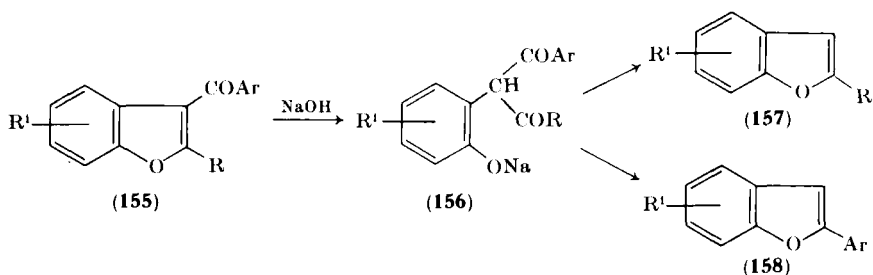
⁴⁰⁰ P. Yates, *J. Amer. Chem. Soc.* **74**, 5376 (1952).

⁴⁰¹ A. Moureu, P. Chovin, and R. Sabourin, *Bull. Soc. Chim. Fr.*, 301 (1956).

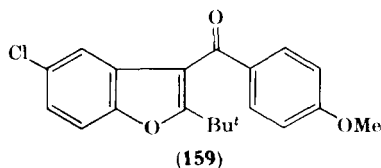
⁴⁰² W. B. Whalley and G. Lloyd, *J. Chem. Soc.*, 3213 (1956).

heating in alkali.^{402,403} Thus, 7-methoxy-3-(2,4,6-trimethoxybenzoyl)-benzofuran gives 7-methoxy-2-(2,4,6-trimethoxyphenyl)benzofuran: ring closure occurs when the alkaline medium is made acidic.

Alkaline degradation of 2-alkyl-3-aroylebenzofurans (**155**) gives in principle, the readily separated compounds **157** and **158**.^{404,405} (cf.



Section IV, A, 3, b). Degradation of 5-chloro-3-(4-methoxybenzoyl)-2-*t*-butylbenzofuran (**159**) forms only 5-chloro-2-(4-methoxyphenyl)benzofuran.²⁵⁷



The synthesis of 2-substituted Bz-acylbenzofurans has been effected using this method: 6-acetyl-2-ethyl-3-(4-methoxybenzoyl)benzofuran is degraded to 6-acetyl-2-ethylbenzofuran and 6-acetyl-2-(4-methoxyphenyl)benzofuran.³⁹⁹

Another method for preparing 2-phenylbenzofurans through *o*-hydroxydeoxybenzoins (without isolating the latter) is the rearrangement of diazoacetophenones with a copper catalyst in the presence of phenol in benzene,⁴⁰⁰ which gives directly 63% phenoxyacetophenone and 26% 2-phenylbenzofuran [Eq. (1)].

o-Methoxydeoxybenzoins (e.g., from 2-methoxyphenylacetic acid with phenol/HF⁴⁰⁶), when treated with HI + MeCOOH,⁴⁰⁰ HBr + MeCOOH,³²⁶ AlCl₃,⁴⁰⁰ or pyridine hydrochloride,^{202,203} are converted

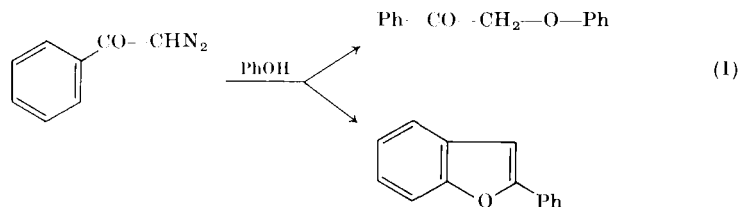
⁴⁰³ W. B. Whalley and G. Lloyd, *Sci. Proc. Roy. Dublin Soc.* **27**, 105 (1956).

⁴⁰⁴ E. Bisagni and R. Royer, *C. R. Acad. Sci.* **250**, 3339 (1960).

⁴⁰⁵ E. Bisagni and R. Royer, *Bull. Soc. Chim. Fr.*, 1968 (1960).

⁴⁰⁶ O. Dann, J. Lang, and H. Vohl, *Justus Liebigs Ann. Chem.* **631**, 116 (1960).

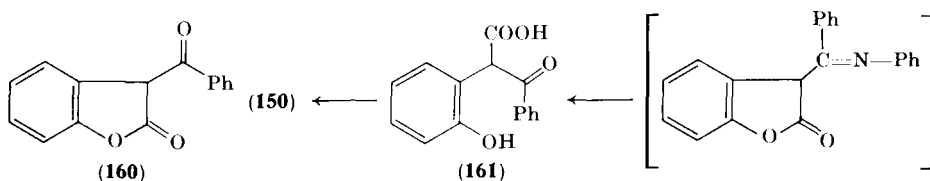
by demethylation and acid-catalyzed ring closure into 2-phenylbenzofurans.



ii. *α-Substituted o-hydroxy and methoxydeoxybenzoins*. With an R³ substituent, the above deoxybenzoins give 2-arylbenzofurans with R³ in position 3, unless they undergo degradation during the reaction.

Reflux of α -cyano-*o*-methoxydeoxybenzoins in HBr + MeCOOH gives an intermediate α -carbonyl compound which is not isolated; the latter is hydrolyzed and decarboxylated to a 2-arylbenzofuran (*o*-tolyl, *m*-tolyl, *p*-tolyl, *p*-chlorophenyl, *p*-hydroxyphenyl).³²⁸

The carbonyl compound (**161**), obtained by hydrolysis of 3-benzoyl-2(3*H*)-benzofuranone (**160**),⁴⁰⁷ gives the benzofuran derivative (**150**) ($R^1 = H$, $R^3 = COOH$, $Ar = Ph$). The same occurs with the product of the “abnormal Chapman rearrangement”³⁹⁵ of *N*-phenylbenzimidazole-2-carboxylic acid (**162**).



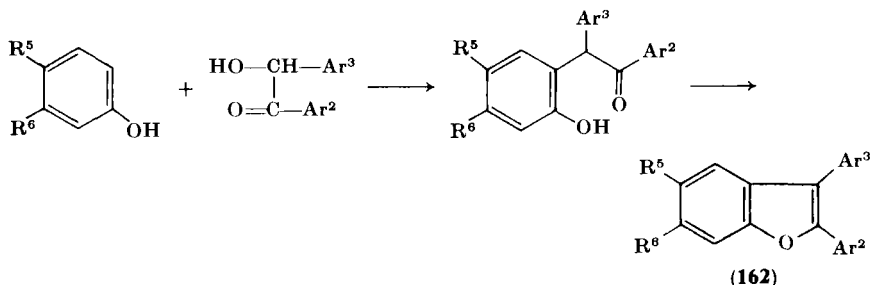
2-Aryl-3-carbomethoxybenzofurans have been obtained.^{408,409} The acid-catalyzed ring-closing dehydration of α -aryldeoxybenzoins gives 2,3-diarylbenzofurans;⁴¹⁰ this is the best method for the synthesis of those compounds (**162**). α -Aryldeoxybenzoins are readily prepared by heating a benzoins with a phenol in dioxan with concentrated HCl.⁴¹⁰

⁴⁰⁷ J. N. Chatterjea, *J. Indian Chem. Soc.* **33**, 175 (1956).

⁴⁰⁸ A. F. Wagner (Merck Co.), U.S. Patent 3,068,265 (1962).

⁴⁰⁹ Y. Kawase, *Bull. Chem. Soc. Jap.* **35**, 573 (1962).

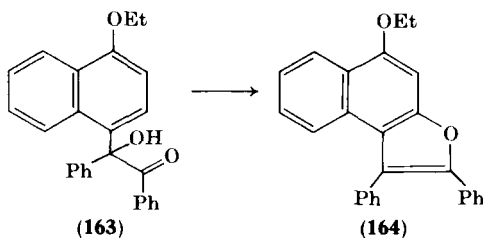
⁴¹⁰ B. R. Brown, G. A. Sommerfeld, and P. D. J. Weitzman, *J. Chem. Soc.*, 4305 (1958).



A range of 2,3-diphenylbenzofurans have thus been obtained.⁴¹⁰⁻⁴¹⁵ Boric acid gives better yields of some 2,3-diphenylbenzofurans.⁴¹²⁻⁴¹⁴

Condensation (dioxan + conc. HCl) of *p*-benzyloxybenzoin with various phenols or naphthols gives 3-(*p*-benzyloxyphenyl)-2-phenylbenzofurans, starting material for the preparation of diarylbenzofurans and of 1,2-diphenylnaphtho[2,1-*b*]furans with "antifertility" activity.⁸³

A special instance of Brown's method is the dehydration of α -(4-ethoxynaphthyl)benzoin (**163**): in the presence of $\text{SnCl}_2 + \text{HCl} + \text{AcOH}$ instead of the normal reduction of the carbonyl group, cyclodehydration occurs, giving 1,2-diphenyl-5-ethoxynaphtho[2,1-*b*]furan (**164**).⁴¹⁶ The reaction also occurs under the influence of H_2SO_4 in AcOH or of AlCl_3 in anisole.



With an unsubstituted 1,3-diphenol and two moles of benzoin, "linear" furo[3,2-*f*]benzofuran derivatives (**165**) are formed.⁴¹⁰ A

⁴¹¹ M. J. Kamlet and J. C. Dalcons, *J. Org. Chem.* **26**, 220 (1961).

⁴¹² A. Wacek and H. Daübner-Rettenbacher, *Monatsh. Chem.* **81**, 266 (1951).

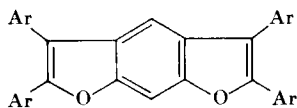
⁴¹³ B. Arventiev and H. Offenberger, *Acad. Repub. Pop. Rom., Filiala Iasi Stud. Cercet. Stiint. Chim.* **11**, 305 (1960); *Chem. Abstr.* **56**, 11554 (1962).

⁴¹⁴ B. Arventiev, H. Wexler, and M. Strul, *Acad. Repub. Pop. Rom., Filiala Iasi Stud. Cercet. Stiint. Chim.* **11**, 63 (1960); *Chem. Abstr.* **55**, 15453 (1961).

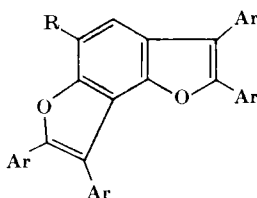
⁴¹⁵ P. K. Grover, H. P. S. Chawla, N. Anand, V. J. Kamboj, and A. B. Kar, *J. Med. Chem.* **8**, 720 (1965).

⁴¹⁶ W. Clowes, *J. Chem. Soc. C*, 1758 (1967).

5-alkylresorcinol gives an "angular" derivative (**165**); phloroglucinol gives a difurobenzofuran.⁴¹⁰



(165)



(166)

e. *Heterocyclic Ring Closure of o-Hydroxylated Aromatic Compounds with Unsaturated Side Chains*

i. *From phenolic allyl ethers.* The allyl ethers of phenols, naphthols, or hydroxylated fused aromatic compounds are rearranged to the corresponding *o*-allyl derivatives (Claisen rearrangement).⁴¹⁷ From the latter, several methods lead to benzofurans. Thus, starting from *o*-allylphenol (**168a**), the reactions shown in Scheme 2 give 2-methyl-2,3-dihydrobenzofuran (**169a**) (pathway A), 2-bromomethyl-2,3-dihydrobenzofuran (**170a**) and 2-methylbenzofuran (**189a**) (pathway B), or 2-hydroxymethyl-2,3-dihydrobenzofuran (**171a**) (pathway C).

Pathway A: from o-allylphenols or allyl ethers of phenols. Allylethers of phenols (**167**) can be converted to 2-alkyl-2,3-dihydrobenzofurans (**169**) (Table IV) directly, by heating compound **167**, (without isolating **168**), with PPA (**167**, $R^5 = \text{OMe}$, $R^7 = \text{Ac}$, $R = R' = R'' = \text{H}$),⁴¹⁸ with pyridine hydrochloride (**167**, $R^4 = \text{Me}$, $R^7 = \text{isoPr}$, $R = R' = R'' = \text{H}$),²⁰⁸ with MgCl_2 at 180° (**167**, $R^7 = \text{NO}_2$, $R = R'' = \text{H}$, $R' = \text{Me}$).⁴¹⁹ Alternatively, **167** gives **169** through the intermediate *o*-allylphenol **168**, by heating at 180° – 220° in the presence of clay (ascanite),⁴²⁹ by treatment with pyridine hydrochloride at 220° – 225° ⁴²⁰ (**168**, $R^5 = t\text{-Bu}$, $R' = R'' = \text{H}$), or in the presence of $\text{ZnCl}_2 + \text{HCl} + \text{AcOH}$ (**168**, $R^1 = R = R' = R'' = \text{H}$), or by heating in $\text{HBr} + \text{AcOH}$ (**168**, $R^1 = R = R' = R'' = \text{H}$)⁴²⁴ (**168**,

⁴¹⁷ S. Patai, "The Chemistry of the Ether Linkage," p. 659. Wiley (Interscience), New York, 1967.

⁴¹⁸ A. O. Fitton and G. R. Ramage, *J. Chem. Soc.*, 2481 (1964).

⁴¹⁹ F. M. C. Co., Netherlands Appl. 6,602,601 (1966); *Chem. Abstr.* **66**, 46319 (1967).

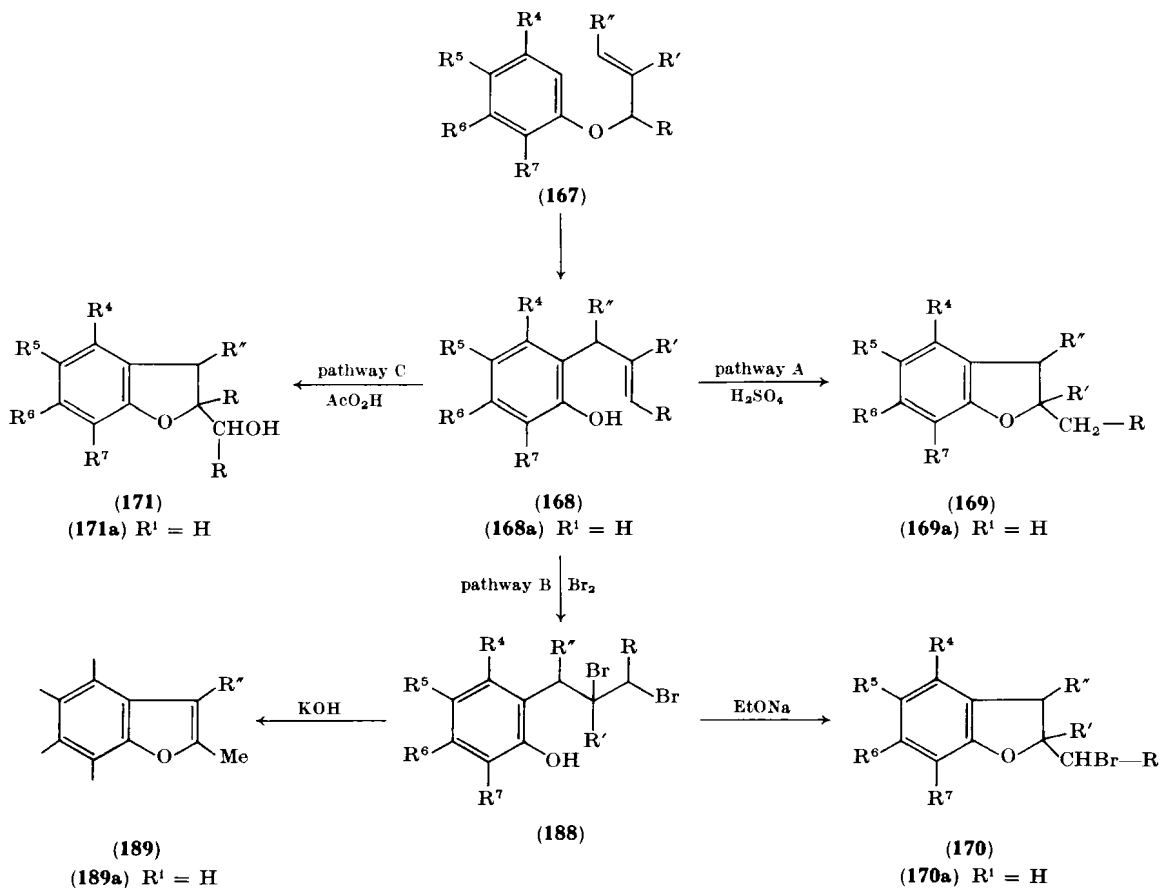
⁴²⁰ A. B. Sen and R. G. Rastogi, *J. Indian Chem. Soc.* **30**, 3558 (1953).

⁴²¹ J. Entel, C. H. Ruof, and H. C. Howard, *J. Amer. Chem. Soc.* **73**, 2365 (1951).

⁴²² R. Dowbenko, Ph. D. Thesis, Univ. of Evanston, Illinois, 1958; *Diss. Abstr.* **19**, 1203 (1958).

⁴²³ Ch. Hurd and R. Dowbenko, *J. Amer. Chem. Soc.* **80**, 4711 (1958).

⁴²⁴ D. S. Tarbell, *Org. React.* **2**, 27 (1944).

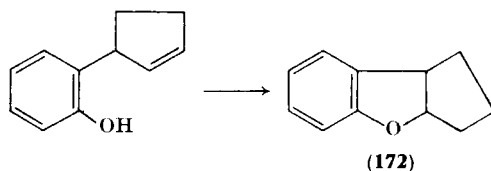


SCHEME 2

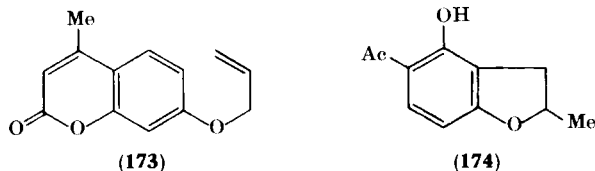
TABLE IV
HETEROCYCLIC RING CLOSURE OF *o*-ALLYL PHENOLS

Compound	Benzofurans, 2,3-dihydro (169)	References	Yield (%)
167			
R ⁵ = OMe, R ⁷ = Ac, R = R' = R'' = H	2-Me, 5-OMe, 7-Ac	418	—
R ⁴ = Me, R ⁷ = isoPr, R = R' = R'' = H	2,4-DiMe, 7-isoPr	208	—
R ⁷ = NO ₂ , R = R'' = H, R' = Me	2,2-DiMe, 7-NO ₂	419	—
R ⁶ = Me, R = R' = R'' = H	2,6-DiMe + 2,4-diMe	295	—
168			
R ⁵ = <i>t</i> -Bu, R = R' = R'' = H	2-Me 5- <i>t</i> -Bu	420	72
R ¹ = R = R' = R'' = H	2-Me	421	52
		424, 425	48-54
R ¹ = H, R = R'' = H, R' = Me	2,2-DiMe	422, 423	87
R ¹ = H, R = R' = H, R'' = Me	2,3-DiMe	422	—
R ⁵ = R ⁷ = Cl, R ⁴ = Me, R = R' = H, R'' = Me	3,4-DiMe, 5,7-diCl	221	—
R ¹ = MeCONH—, R = R'' = H R' = Me	2,2-DiMe, R ¹ = MeCONH—	90	—
R ⁷ = OMe, R = R'' = H, R' = Me	2,2-DiMe, 7-OMe	426	90
R ⁵ = Cl, R ⁷ = OMe, R = R'' = H, R' = Me	2,2-DiMe, 5-Cl 7-OMe	426	90
R ⁶ = OMe, R = R' = R'' = H	2-Me, 6-OH	427	—
R ⁵ = OMe, R = R' = R'' = H	2-Me, 5-OMe	427	—
R ⁴ = R ⁶ = OMe, R = R' = R'' = H	2-Me, 4,6-diOMe	10	—
R ⁶ = OMe, R = R' = R'' = H R ⁷ = <i>p</i> -CO—C ₆ H ₄ —Cl	2-Me, 6-OMe, 7-(<i>p</i> -CO—C ₆ H ₄ Cl)	428	—
R ⁷ = Me, R ¹ = H	2,7-DiMe	321	24
R ⁷ = OMe, R ¹ = H	2-Me, 7-OMe	321	11.6
R ⁷ = OEt, R ¹ = H	2-Me, 7-OEt	321	18

$R^5 = R^7 = \text{Cl}$, $R^4 = R'' = \text{Me}$, $R = R' = \text{H}$).²²¹ When applied to 2-cyclopenten-3-yl phenol, compound **172** is obtained.⁴³⁰



A more involved example, leading to a 2-methylbenzofuran derivative, is that of 7-hydroxy-4-methylcoumarin, which is converted to the 7-allyloxy derivative (**173**) and gives in one stage (concentrated H_2SO_4) the 2,3-dihydrobenzofuran (**174**) (ring closure followed by opening of the lactone ring).⁴³¹



While treatment in $\text{HBr} + \text{AcOH}$ by the Tarbell method⁴²⁴ leads directly from allylphenols **168** to compounds **169**, other methods involve the formation of the brominated derivative obtained by adding HBr (in the presence of diphenylamine) to the allylphenol.⁴³² Ring closure is effected by sodium ethoxide. Thus, the 11*H*-furo[3,2-*a*]xanthone derivative (**177**) can be obtained either directly from the allyl derivative (**175**) or via the bromo derivative (**176**).^{432,433} Similarly, **179** has been obtained from the chromone **178**.⁴³⁴

⁴²⁵ A. O. Fitton and R. K. Smalley, "Practical Heterocyclic Chemistry," p. 16. Academic Press, New York, 1968.

⁴²⁶ J. Gillon (Fisons Pest. Control. Ltd), South Africa Patent 6,705,116 (1968); *Chem. Abstr.* **70**, 87555 (1969).

⁴²⁷ N. S. Narasimhan and M. V. Paradkar, *Indian J. Chem.* **7**, 1004 (1969).

⁴²⁸ A. A. Shamsburin and L. P. Sinyavskaya, *Zh. Org. Khim.* **6**, 1682 (1970); *Chem. Abstr.* **73**, 98547 (1970).

⁴²⁹ E. D. Laskina, T. A. Rudol'fi, and N. N. Belov, *Zh. Obshch. Khim.* **33**, 2513 (1963); *Chem. Abstr.* **60**, 491 (1964).

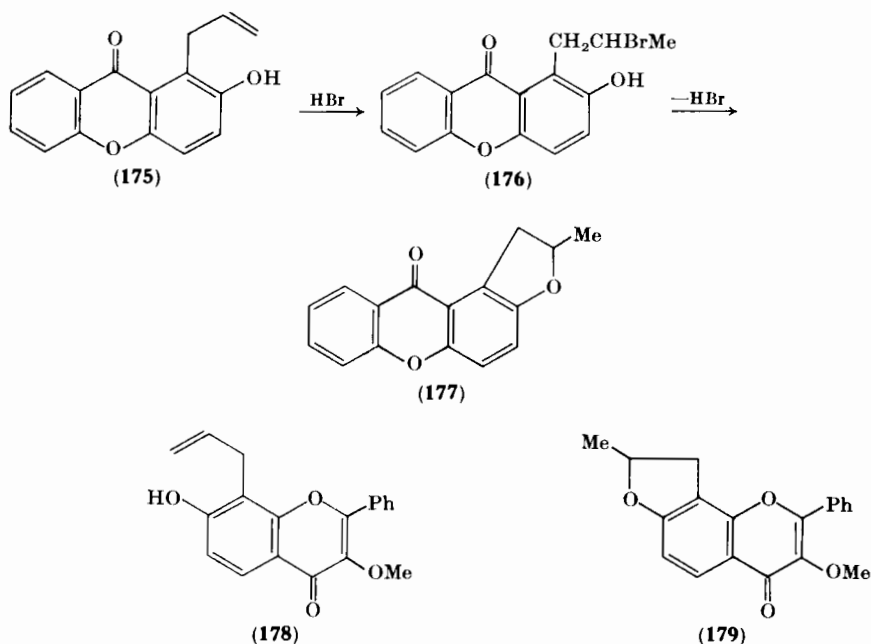
⁴³⁰ A. R. Bader, *J. Amer. Chem. Soc.* **75**, 5967 (1953).

⁴³¹ J. J. Chi and M. Hu, *J. Chim. Soc.* **17**, 144 (1950); *Chem. Abstr.* **47**, 3293 (1953).

⁴³² F. Scheinmann and H. Suschitzky, *Tetrahedron* **7**, 31 (1959).

⁴³³ A. Mustafa, M. M. Sidky, S. M. A. Zayed, and F. M. Soliman, *Tetrahedron* **19**, 1335 (1963).

⁴³⁴ S. S. Chibber, A. K. Ganguli, S. K. Mukerjee, and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A* **46**, 19 (1957); *Chem. Abstr.* **52**, 4617 (1958).



The Bz-hydroxylated 2,3-dihydrobenzofuran derivatives required for the synthesis of several natural substances have been obtained by this method: 4-allyl-1,3-dimethoxybenzene gives (HBr/HOAc with demethylation) 6-hydroxy-2-methyl-2,3-dihydrobenzofuran.⁴²⁷ 2-Allyl-4-methoxyphenol and 2-allyl-3,5-dimethoxyphenol lead, respectively, to 5-methoxy-2-methyl-2,3-dihydrobenzofuran and 4,6-dimethoxy-2-methyl-2,3-dihydrobenzofuran (without demethylation).

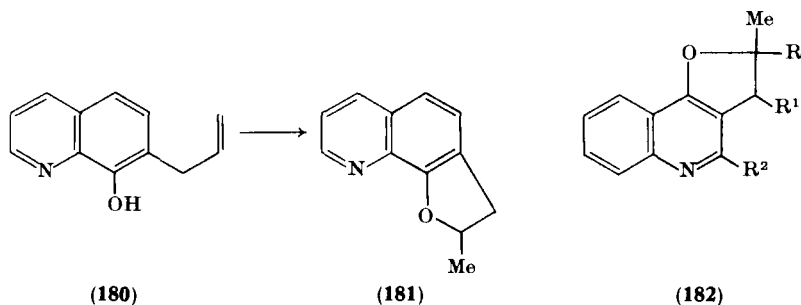
The ring closure of *o*-allyl phenols has been extended to the synthesis of several other types of fused furans.

Naphthofurans have been synthesized from the corresponding naphthols: thus 2-methoxy-3-allylnaphthalene (from allyl bromide and 3-lithio-2-methoxynaphthalene) gives 2-methyl-2,3-dihydronaphtho[2,3-*b*]furans,⁴³⁵ and 1-allyl-2-naphthol gives (with pyridine hydrochloride) 2-methyl-2,3-dihydronaphtho[2,1-*b*]furan.⁴³⁶

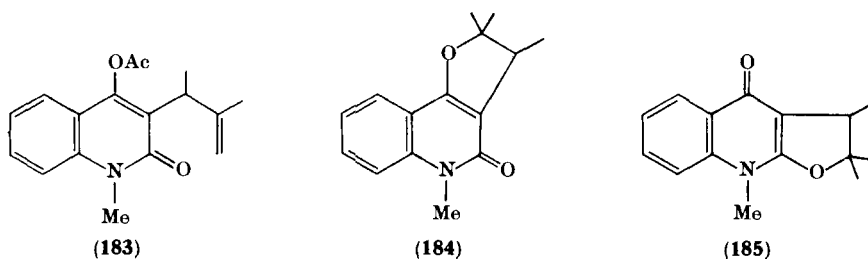
Furoquinolines have been obtained by ring closure (H_2SO_4) of *o*-hydroxylated Bz-allylquinolines (180) (to give, e.g., 2-methyl-2,3-dihydrofuro[2,3-*h*]quinoline, 181).²²³ Crotyl ethers give the corresponding 2,3-dimethyl derivatives.²²³ This method has provided the

⁴³⁵ N. S. Narasimhan and M. V. Paradkar, *Indian J. Chem.* **7**, 536 (1969).

⁴³⁶ K. Takeda and H. Osaka, *J. Pharm. Soc. Jap.* **75**, 210 (1955); *Chem. Abstr.* **45**, 1574 (1956).



isomeric dihydrofuroquinolines of type **182**⁴³⁷ (which could not be synthesized by other methods²³¹) either by heating with pyridine hydrochloride (e.g., **182**, R = R¹ = H, R² = Me)^{438,439} or by means of H₂SO₄ at low temperatures.²³¹



In the furoquinoline series, Tarbell's technique may also be used: 4-acetoxy-1-methyl-3-(1,2-dimethyl-2-propenyl)-2-quinolone (**183**), obtained by an abnormal Claisen reaction⁴⁴⁰ and treated with HBr + AcOH at 20° for 26 hours, gives a mixture of the isomeric furoquinolines **184** and **185**.

Finally, for benzofuro-benzopyrans, concentrated sulfuric acid has been used for the ring closure of **186** to **187**.⁴⁴¹ Other instances have been mentioned recently.⁴⁴²

Pathway B: from o-(2,3-dibromopropyl)phenol derivatives (188). The addition of one molecule of bromine to *o*-hydroxylated allyl derivatives

⁴³⁷ N. S. Narasimhan and M. V. Paradkar, *Chem. Ind. (London)*, 831 (1967).

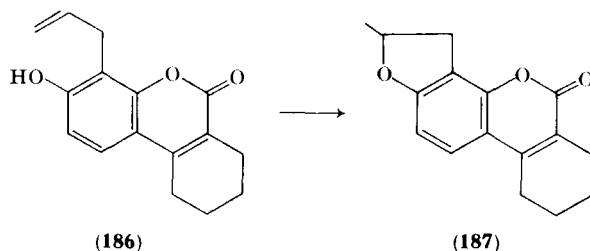
⁴³⁸ H. Kano and Y. Makisumi (Shionogi and Co. Ltd.), French Patent M 3234 (1955); *Chem. Abstr.* **63**, 18090 (1965).

⁴³⁹ Y. Makisumi, *Chem. Pharm. Bull.* **12**, 789 (1964); *Chem. Abstr.* **61**, 9461 (1964).

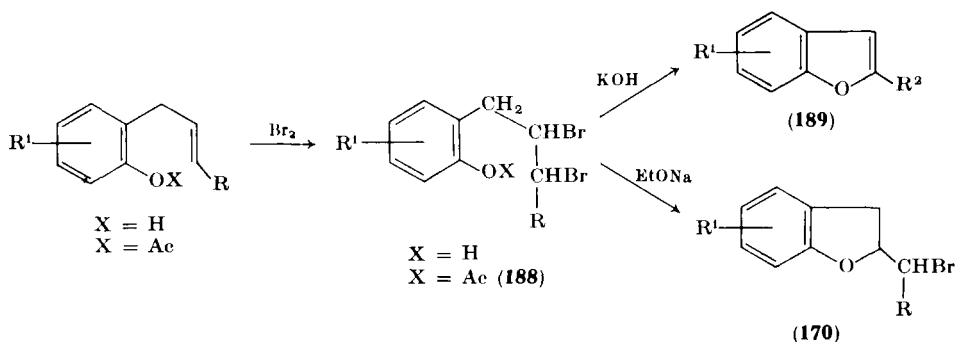
⁴⁴⁰ T. R. Chamberlain and M. J. Grundon, *J. Chem. Soc. C*, 910 (1971).

⁴⁴¹ M. G. Parekh and N. K. Trivedi, *Aust. J. Chem.* **23**, 407 (1970); *Chem. Abstr.* **72**, 90208 (1970).

⁴⁴² N. H. Pardanani and K. N. Trivedi, *J. Indian Chem. Soc.* **49**, 283 (1972).



readily gives the corresponding 2,3-dibromopropyl derivatives (Scheme 3). Prolonged heating with excess alkali gives 2-alkylbenzofurans (189) by the Kaufman method:⁴⁴³ *o*-(2,3-dibromopropyl)phenyl acetate (188, X = Ac, R¹ = R = H) is converted into 2-methylbenzofuran (189, R¹ = H, R² = Me) with 5% of the isomeric 2*H*-chromene.²⁷⁶



SCHEME 3

The method is used chiefly for preparing more complex benzofuran derivatives. Thus, coumarins (190) lead to furobenzopyranones (191),³¹² and xanthenes to furoxanthenes 192^{444,445} and 193.⁴⁴⁶

Treatment of the dibromides with sodium ethoxide gives 2-bromomethyl-2,3-dihydrobenzofurans (170): *o*-(2,3-dibromopropyl)phenyl acetate (188, X = OAc, R = H) gives 2-bromomethyl-2,3-dihydrobenzofuran (170, R = R¹ = H).⁴⁴⁷ The following substituted 2-bromomethyl-2,3-dihydrobenzofurans have been prepared by this method:

⁴⁴³ K. D. Kaufman, *J. Org. Chem.* **26**, 117 (1961).

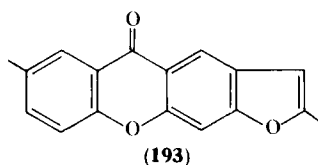
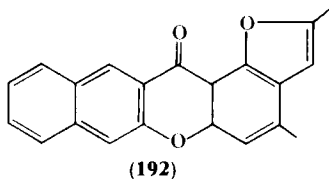
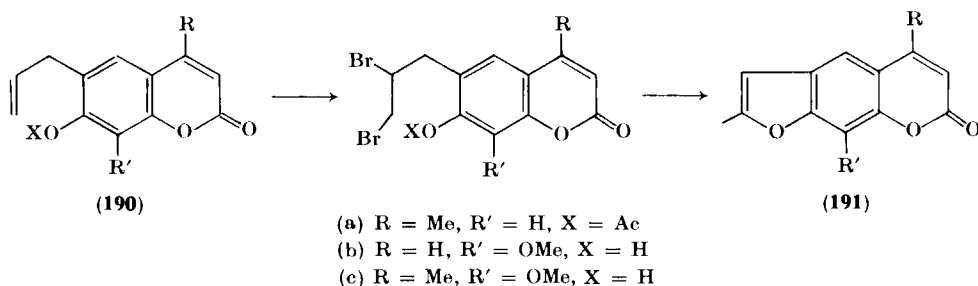
⁴⁴⁴ A. N. Goud and S. Rajagopal, *Proc. Indian Acad. Sci., Sect. A* **69**, 129 (1969); *Chem. Abstr.* **72**, 3318 (1970).

⁴⁴⁵ A. N. Goud and S. Rajagopal, *Tetrahedron* **23**, 4791 (1967).

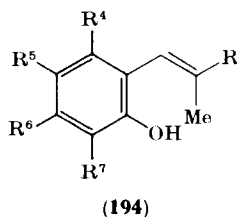
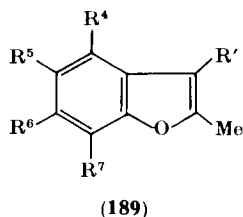
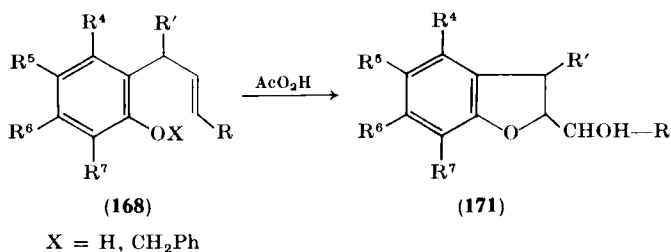
⁴⁴⁶ Y. S. Agasimundin and S. Rajagopal, *Monatsh. Chem.* **97**, 423 (1966).

⁴⁴⁷ C. M. Foltz, Ph. D. Thesis, Univ. Purdue, 1954.

5-methyl, 7-methyl, 5-chloro, 7-chloro, 5-methoxy,^{448,449} and 5-phenoxy 7-phenoxy.⁴⁵⁰



Pathway C: Synthesis of 2-(1-hydroxyalkyl)benzofuran derivatives from o-alkenylphenols. *o*-Alkenylphenols and their benzyl ethers (**168**), treated with a peroxy acid, give epoxides which, according to conditions, lead



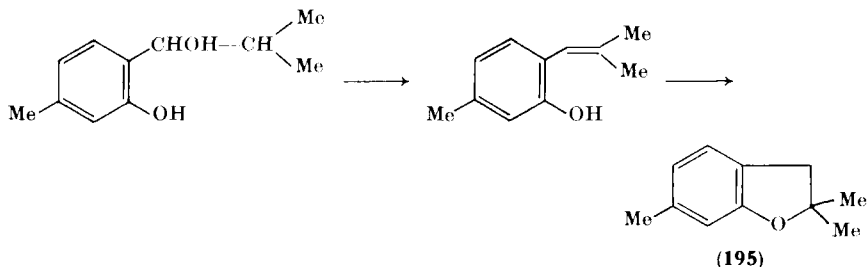
⁴⁴⁸ S. Toyoshima, N. Hirose, T. Ogo, and A. Suggii, *Yakugaku Zasshi* **88**, 503 (1968); *Chem. Abstr.* **69**, 106373 (1968).

⁴⁴⁹ S. Toyoshima, N. Hirose, T. Ogo, and A. Suggii, *Yakugaku Zasshi* **87**, 1548 (1967); *Chem. Abstr.* **69**, 106372 (1968).

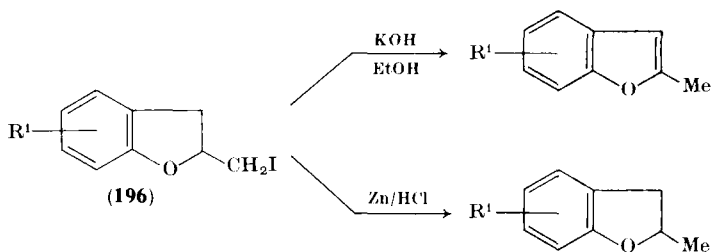
⁴⁵⁰ A. Funke and K. V. Daniken, *Bull. Soc. Chim. Fr.*, 457 (1953).

either to 2-(1-hydroxyalkyl)-2,3-dihydrobenzofuran derivatives (**171**) or to 2-methylbenzofuran derivatives (**189**). *o*-Propenylphenols (**194**), readily obtained from *o*-allylphenols by isomerization, give *o*-(1,2-epoxypropyl)phenols, then, by treatment with H_2SO_4 , 2-methylbenzofurans⁴⁵² (Table V).

ii. *Heterocyclic ring closure of o-alkenyl phenols by various methods.* A method that can be looked upon as a heterocyclic ring closure of *o*-propenylphenols gives 2,2-dialkyl-2,3-dihydrobenzofurans (**195**) in one stage from phenols and 2,2-disubstituted aldehydes. The reaction was extended to a variety of polyalkyl phenols and α -naphthols.⁴⁵⁴



Iodine ring closure of o-allylphenols. Treatment with iodine chloride (in ethanol or CCl_4) of *o*-allylphenols gives 2-iodomethyl-2,3-dihydrobenzofurans (**196**).⁴⁵⁵⁻⁴⁵⁷ The latter compounds can lead either to the



⁴⁵¹ V. I. Pansevich-Kolyada and Z. B. Idel'chik, *Zh. Obshch. Khim.* **25**, 2215 (1955); *Chem. Abstr.* **50**, 9370 (1956).

⁴⁵² V. I. Pansevich-Kolyada and Z. B. Idel'chik, *Zh. Obshch. Khim.* **24**, 807 (1954), *Chem. Abstr.* **49**, 8183 (1955).

⁴⁵³ B. I. Nurunnabi, *Pakistan J. Sci. Ind. Res.* **3**, 108 (1960); *Chem. Abstr.* **55**, 25903 (1961).

⁴⁵⁴ J. C. Martini, N. W. Franke, and G. M. Singerman, *J. Org. Chem.* **35**, 2904 (1970).

⁴⁵⁵ D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *J. Org. Chem.* **31**, 2192 (1966).

⁴⁵⁶ N. H. Pardani and K. N. Trivedi, *Aust. J. Chem.* **25**, 1537 (1972).

⁴⁵⁷ V. I. Staninets and E. O. Shilov, *Dopov. Akad. Nauk. Ukr. SSR*, 1474 (1962); *Chem. Abstr.* **59**, 2754 (1963).

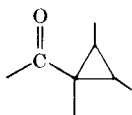
TABLE V
SYNTHESIS OF 2-(1-HYDROXYALKYL)-2,3-DIHYDROBENZOFURANS FROM *o*-ALLYL PHENOLS (**168**) AND
o-PROPENYL PHENOLS (**194**)

Starting compound	Reagent	Benzofuran	Yield (%)	References
a. 168 (X = H)				
R ¹ = H	AcO ₂ H, 12 hours, 20–30°	2,3-Dihydro 2-CH ₂ OH	40	324
R = Me, R ¹ = H	AcO ₂ H, 12 hours, 20–30°	2,3-Dihydro 2-CHOH—Me	—	324
R ⁶ = Me, R ¹ = H	1. AcO ₂ H 2. H ₂ SO ₄	2,6-DiMe	—	451
R ⁵ = Me R ¹ = H	H ₂ SO ₄	2,5-DiMe	—	451
b. 168 (X = CH ₂ Ph)				
R ¹ = H	1. AcO ₂ H 2. EtONa, EtOH	2,3-Dihydro 2-CH ₂ OH	60	453
R ⁶ = OMe R ¹ = H	EtONa, EtOH	2,3-Dihydro 2-CH ₂ OH 6-OMe	—	453
c. 194				
R ¹ = H	1. AcO ₂ H	2-Me	—	452
R ⁷ = Me	2. H ₂ SO ₄	2,7-DiMe	—	452

corresponding 2-methylbenzofurans (10% KOH in ethanol) or to 2-methyl-2,3-dihydrobenzofurans (Zn + HCl).⁴²⁰ Similarly, *o*-allylphenol with Adams's reagent ($\text{HgCl}_2 + \text{I}_2$) gives compound (196) ($\text{R}^1 = \text{H}$).³²⁴

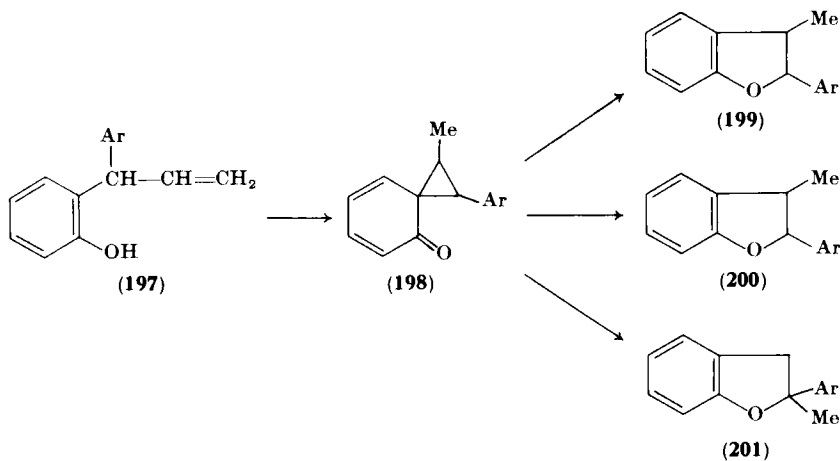
2-Iodomethyl-2,3-dihydrobenzofurans (196) and the corresponding 2-iodomercurimethyl derivatives can be obtained from *o*-allylphenols and mercuric acetate, via the 2-acetoxymercuri-2,3-dihydrobenzofurans.⁴²⁰

iii. *Heterocyclic ring closure of cyclopropyl ketones and esters.* A number of methods with miscellaneous starting points have in common the formation of the benzofuran ring from the following structural element:



Photochemical rearrangement of 2-(1-arylallyl) phenols. Various instances of rearrangement found in the course of thermal, chemical, and photochemical ring closure of 2-(1-arylallyl) phenols have recently been described.⁴⁵⁸

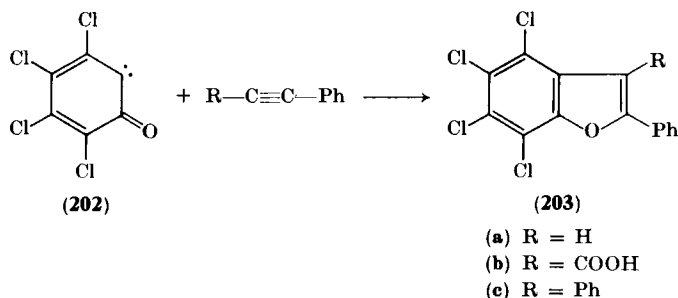
Thus, 2-(1-arylallyl) phenols **197** are converted into compounds **199** by heating in dimethylaniline, into a mixture of **199**, **200**, and **201** by acid ($\text{HBr} + \text{MeCOOH}$), and into compounds **200** by irradiation. Under



⁴⁵⁸ E. Schmid, G. Frater, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta* **55**, 1625 (1972).

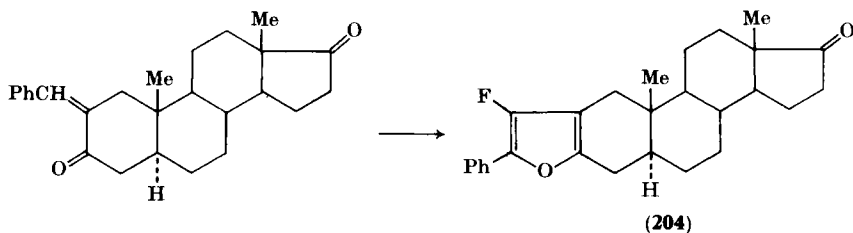
the last conditions, **199** is also converted into **200**. The proposed mechanism involves the intermediate compound **198**.

Addition of carbenes. Arylacetylenes condense with the chlorinated oxocarbene **202** (35 hours at 100°) and give, through 1,3-cycloaddition, 3-substituted 4,5,6,7-tetrachloro-2-phenylbenzofurans (**203**).⁴⁵⁹ Compound **203** is readily dechlorinated (hydrogenation on Raney nickel in



20% methanol-KOH) to 2-phenylbenzofuran. The reaction has been extended to the condensation of oxocarbene (**202**) with various unsaturated compounds: styrene, stilbenes, ethyl fumarate, ethyl maleate, ethyl cinnamate.⁴⁶⁰

In the same way, the reaction of difluorocarbene on 2-benzylidene-cyclohexanone gives 3-fluoro-2-phenyl-4,5,6,7-tetrahydrobenzofuran (with evolution of HF).⁴⁶¹ This method has been applied to the synthesis of furosteroids (**204**).⁴⁶¹



A similar method involves the reaction of difluorocarbene on enones⁴⁶² or on Mannich bases (**205**) with formation of furosteroids (**206**).⁴⁶³

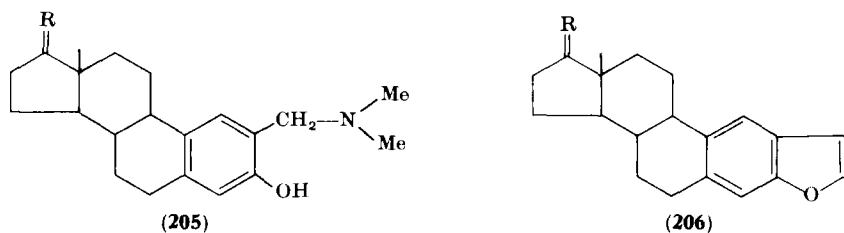
⁴⁵⁹ R. Huisgen, G. Binsch, and H. Koenig, *Chem. Ber.* **97**, 2884 (1964).

⁴⁶⁰ C. Binsch, R. Huisgen, and H. Koenig, *Chem. Ber.* **97**, 2893 (1964).

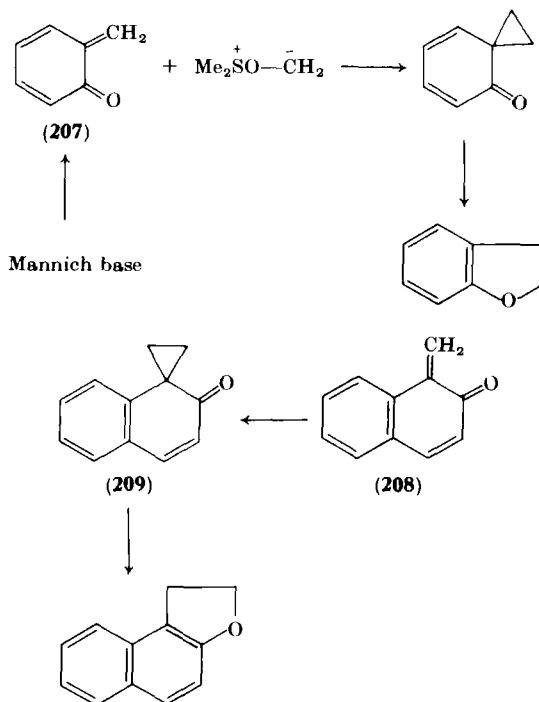
⁴⁶¹ P. Hodge and M. Derenberg, *J. Chem. Soc. D*, 233 (1971).

⁴⁶² P. Hodge, J. Edwards, and S. H. Fried, *Tetrahedron Lett.*, 5176 (1966).

⁴⁶³ H. G. Lehmann, *Tetrahedron Lett.*, 607 (1968).



The same intermediate occurs in the *Lehmann method*⁴⁶³ for converting the methiodides of phenolic Mannich bases into 2,3-dihydrobenzofurans, through reaction with dimethyloxosulfonium methylide. Thus, *o*-benzoquinone methide (**207**) leads to 2,3-dihydrobenzofuran according to Scheme 4. Similarly, 2-naphthol gives 1,2-dihydronaphtho[2,1-*b*]furan through **208** and **209**, formed and rearranged *in situ*.⁴⁶⁴ The reaction has been applied to the synthesis of polycyclic benzofurans.^{463,465}

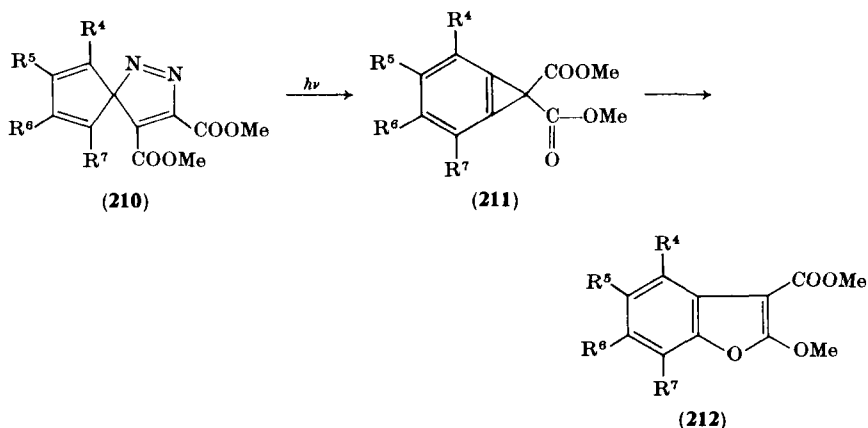


SCHEME 4

⁴⁶⁴ L. Breuer and D. Melumad, *Tetrahedron Lett.*, 1875 (1969).

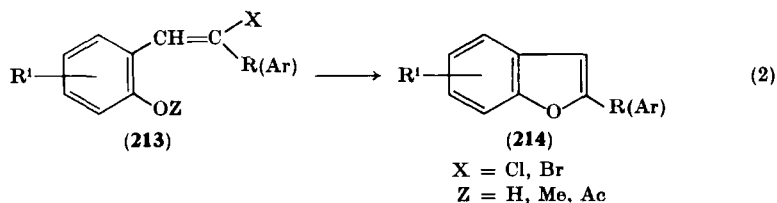
⁴⁶⁵ W. W. Sullivan, D. Ullman, and S. Schechter, *Tetrahedron Lett.*, 457 (1969).

Finally, the cyclopentadienespiropyrazoles (**210**) are photolyzed to 1*H*-cyclopropabenzenes (**211**); thermolysis of the latter (15 minutes at 170°) leads to the corresponding tetrasubstituted 2-methoxy-3-carbomethoxybenzofurans (**212**).⁴⁶⁶



iv. *Photochemical creation of the benzofuran ring.* The literature provides several instances of the formation of benzofurans or of 2,3-dihydrobenzofurans by photochemical ring closure of *o*-allylphenol,^{467,468} 2-allyl-*p*-benzoquinones,^{469,470} and substituted cyclohexadienones (synthesis of 2-bromomethyl-4,7-di-*t*-butyl-2,3-dihydrobenzofuran).⁴⁷¹

*Heterocyclic ring closure of *o*-hydroxylated or *o*-acylated styrene, stilbene, and stilbazole derivatives.* This group includes miscellaneous methods, the final stage of which involves ring closure of compounds as in Eq. (2). Starting from *o*-acyloxystilbenes, the reaction provides



⁴⁶⁶ H. Dürr and L. Schrader, *Chem. Ber.* **103**, 1334 (1970).

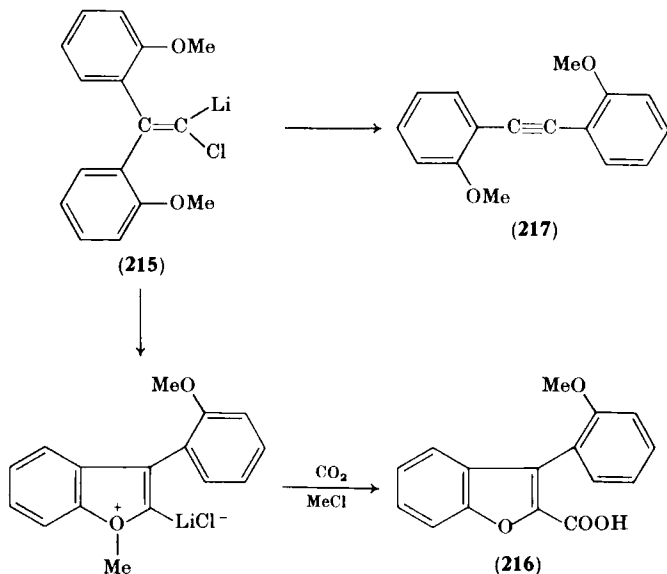
⁴⁶⁷ G. Frater and H. Schmid, *Helv. Chim. Acta* **50**, 255 (1967).

⁴⁶⁸ W. M. Horspool and P. L. Panson, *Chem. Commun.*, 195 (1967).

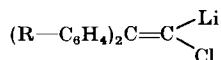
⁴⁶⁹ C. M. Orlando, H. Merk, A. K. Bose, and M. S. Mankes, *J. Amer. Chem. Soc.* **89**, 6527 (1967).

⁴⁷⁰ M. Orlando, H. Merk, A. K. Bose, and M. S. Mankes, *J. Org. Chem.* **33**, 2512 (1968).

2-arylbenzofurans. Applied to stilbazole (Ar = pyridyl) it gives 2-pyridylbenzofurans⁴⁷² (e.g., 2-(4-pyridyl)benzofuran or pyridarone, with neurodepressing action).



Thermal ring closure of a (1-chloro-2,2-diarylvinyllithium with the general formula



normally gives a 1,2-diarylacetylene (Fritsch-Battenberg-Wiechell rearrangement). In the case of compounds **215**, the benzofuran derivative (**216**) is obtained in 14% yield, together with the expected 2,2-dimethoxydiphenylacetylene (**217**).⁴⁷³

The Nikl reaction⁴⁷⁴ (alkylation of dimedone by 1,4-dibromo-2-methyl-2-butene, with formation of compound **218**), applied to phloroacetophenone and to 3-isopentyl-2,4,6-trihydroxyisobutyrophenone, leads respectively to 2,3-dihydrobenzofurans **219a** and **219b**. Furan **219b** with toluene-*p*-sulfonic acid rearranges to the benzofuran **220b**.⁴⁷⁵

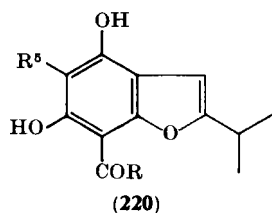
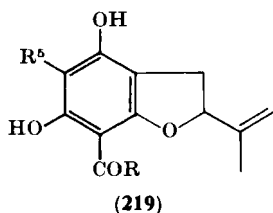
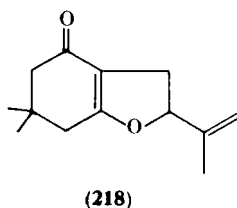
⁴⁷¹ B. Muller, *Chem. Commun.*, 327 (1966); *Chem. Abstr.* **65**, 7124 (1966).

⁴⁷² A. Ziegler, H. Inion, G. Aussems, A. Christiaens, F. Chaillet, and R. Charlier, *Chim. Ther.* **6**, 159, (1971).

⁴⁷³ G. Kobuch and F. H. Trapp, *Chem. Ber.* **99**, 680 (1966).

⁴⁷⁴ J. Nikl, *Chem. Ber.* **91**, 553 (1958).

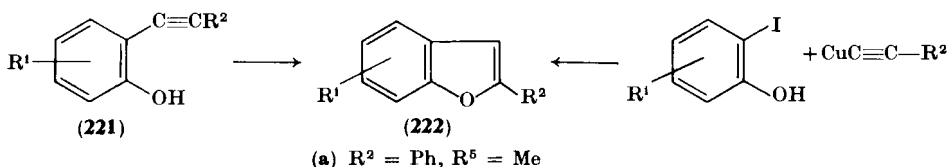
⁴⁷⁵ D. M. Cahill and P. V. R. Shannon, *J. Chem. Soc. C*, 938 (1969).



- (a) $R^5 = H$
 (b) $\begin{cases} R^5 = (CH_2)_2-CHMe_2 \\ R = CHMe_2 \end{cases}$

1,1-Dichloro-2-butylcyclopropane, heated at 180° with excess phenol, gives 3-butyl-2-methylbenzofuran (low yield); 7,7-dichlorobicyclo[4,1,0]heptane gives 2,3-pentamethylenebenzofuran (70% yield); 1,1-dichloro-2-phenylcyclopropane gives 3-methyl-2-phenylbenzofuran (74% yield).^{476,477}

v. *Heterocyclic ring closure of o-hydroxylated aromatic compounds with acetylenic side chains.* This method leads from acetylenic compounds **221** to 2-substituted benzofurans **222**. Thus, 1-(2-hydroxy-5-methyl)phenyl-2-phenylacetylene (**221a**), heated at 90° for 45 minutes in the presence of 2 N NaOH, gives 5-methyl-2-phenylbenzofuran (**222a**) (90% yield).⁴⁷⁸



Silver *o*-hydroxyphenylacetylide in water is ring-closed to benzofuran (54% yield) by UV rays at room temperature.⁴⁷⁹ Similarly, oxidizing *o*-hydroxyphenylacetylene (**221**, $R^1 = H$) in the presence of NaOEt forms 2,2'-bisbenzofuranyl and 2-(*o*-hydroxyphenylethynyl)benzofuran besides the diacetylene.⁴⁸⁰

Benzofurans **222** are obtained in one stage by heating an iodinated phenol with copper phenylacetylide in pyridine at 125° under nitrogen

⁴⁷⁶ G. L. Robinson, U.S. Patent 3,230,237 (1966); *Chem. Abstr.* **64**, 11176 (1966).

⁴⁷⁷ G. L. Robinson, *J. Org. Chem.* **32**, 3218 (1967).

⁴⁷⁸ F. Wessely and E. Zbiral, *Justus Liebigs Ann. Chem.* **605**, 98 (1957).

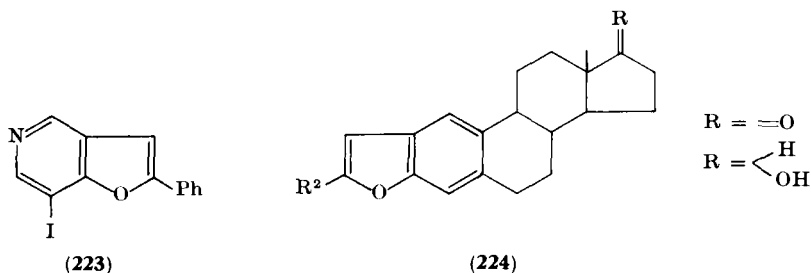
⁴⁷⁹ V. Frey and G. Pieh, *Monatsh. Chem.* **80**, 791 (1950).

⁴⁸⁰ F. Toda and M. Nakagawa, *Bull. Chem. Soc. Jap.* **32**, 514 (1959); *Chem. Abstr.* **54**, 3366 (1960).

TABLE VI
 BENZOFURANS FROM *o*-HYDROZYPHENYLACETYLENES

Starting compounds				
Phenols or other hydroxylated (or potential hydroxylated) compounds	Cuprous acetylide (R ²)	Benzofurans (222)	Yield (%)	References
<i>o</i> -Iodophenol	<i>n</i> -Pr	2- <i>n</i> -Pr	42	482, 483
<i>o</i> -Iodophenol	Ferrocenyl	2-Ferrocenyl	—	484
2,4-Dibromophenol	<i>n</i> -Pr	2- <i>n</i> -Pr 5-Br	—	482, 483
2,4-Dibromophenol	Ph	2-Ph 5-Br	—	482, 483
2,4-Dibromophenol	2-Pyridyl	2-(2-Pyridyl) 5-Br	38	482, 483
3,5-Diiodo-4-pyridone	Ph	223	—	483
2-Iodoestrone	Aryl or alkyl	224	—	485
2-Bromo-5,5-dimethyl-cyclohexane-1,3-dione	Ph	4-Oxo-2-Ph-6,6-diMe 4,5,6,7-Tetrahydro	—	486

(85% yield).⁴⁸¹ Generalizing this method (Table VI) has led to simple benzofurans **222**^{482,483} to their nitrogenated analogs (e.g., **223**, 7-iodo-2-phenylfuro[3,2-*c*]pyridine),⁴⁸³ to polycyclic benzofuran derivatives (e.g., **224**⁴⁸⁵), and to tetrahydrobenzofurans.⁴⁸⁶



The synthesis of 2-arylbenzofurans **226** by heterocyclic ring closure of acetylenic compounds **225** with pyridine hydrochloride is a variation⁴⁸⁷ of the general method of heterocyclic ring closure of acetylenic compounds **221**.

⁴⁸¹ C. E. Castro and R. D. Stephens, *J. Org. Chem.* **28**, 2163 (1963).

⁴⁸² R. D. Stephens and C. E. Castro, *J. Org. Chem.* **28**, 3313 (1963).

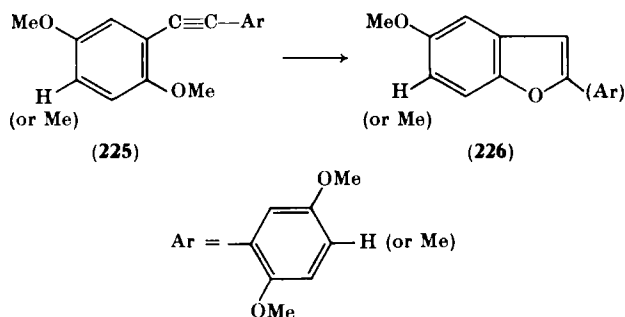
⁴⁸³ C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.* **31**, 4071 (1966).

⁴⁸⁴ M. D. Rausch and A. Siegel, *J. Org. Chem.* **34**, 1974 (1969).

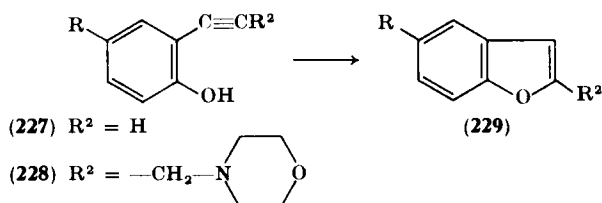
⁴⁸⁵ M. Stefanovic, L. Krstic, and S. Mladenovic, *Tetrahedron Lett.*, 3312 (1971).

⁴⁸⁶ K. Gump, S. W. Moje, and C. E. Castro, *J. Amer. Chem. Soc.* **89**, 6771 (1967).

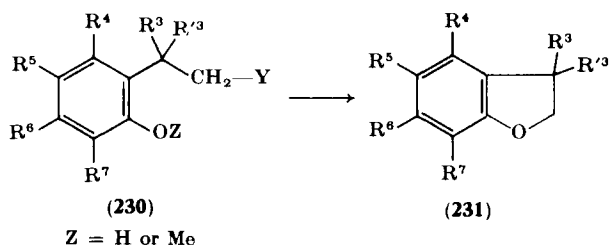
⁴⁸⁷ G. Manecke and D. Zefner, *Chem. Ber.* **105**, 1943 (1972).



Mannich condensation of *o*-hydroxyphenylacetylene (**227**, R = H) leads to compound **228**; heterocyclic ring closure of the latter gives the basic 2-substituted benzofuran **229**. The diacetylenic derivative (**227**, R = C≡CH) gives the corresponding 5-ethynylbenzofuran (**229**, R = C≡CH).⁴⁸⁸



f. Heterocyclic Ring Closure of Hydroxylated Aromatic Compounds with Saturated Side Chains. In this generalization of the Stoermer-Kahlert reaction (1901) the starting molecule has the general formula **230**. Treatment with an alkali (Y = Br)⁴⁸⁹⁻⁴⁹¹ or with a dehydrating medium (toluene-*p*-sulfonic acid in benzene) (Y = OH)⁴⁹² provides a



⁴⁸⁸ N. L. Kotlyarevskii, R. N. Maysnikova, and M. Bardamova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1**, 202 (1971); *Chem. Abstr.* **75**, 5594, (1971).

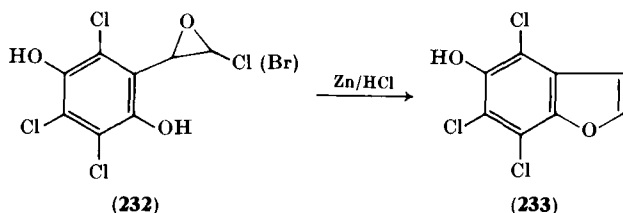
⁴⁸⁹ G. Chatelus, Thesis, Strasbourg, 1947; *Ann. Chim. (Paris)* **4**, 505 (1949).

⁴⁹⁰ P. Cagniant, *C. R. Acad. Sci.* **229**, 889 (1949).

⁴⁹¹ P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 931 (1955).

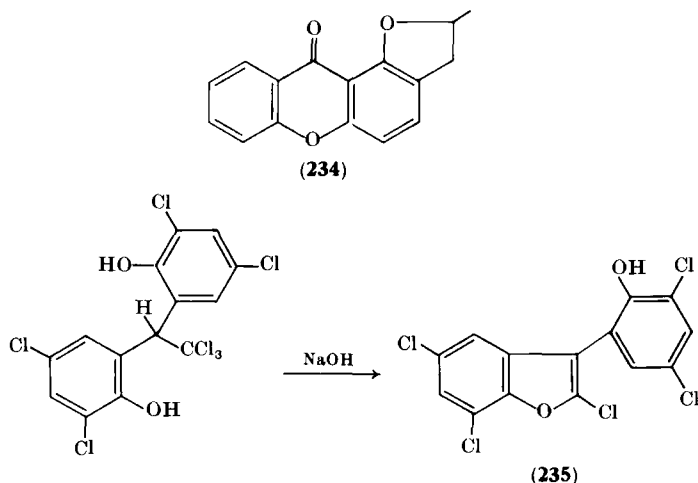
⁴⁹² J. Colonge and G. Descartes, *C. R. Acad. Sci.* **246**, 777 (1958).

simple method for preparing 2,3-dihydrobenzofurans **231**. In some instances, benzofurans are obtained (e.g., **233**).⁴⁹³ The tosyl⁴⁹⁴ or the



phthaloyl⁴⁹⁵ esters of alcohols (**230**) (Y = OH) may also be used as starting materials.

These methods have been applied to the synthesis of dihydronaphtho-[1,2-*b*], [2,1-*b*], and [2,3-*b*] furans and their substituted derivatives,^{491,496-499} and of the furoxanthone (**234**).⁵⁰⁰ A special case is the preparation of the benzofuran (**235**) as shown.⁵⁰¹



⁴⁹³ E. P. Prudchenko and E. P. Fokin, *Izv. Sib. Otd. Akad. Nauk. SSSR, Ser. Khim. Nauk*, 106 (1971); *Chem. Abstr.* **77**, 48119 (1972).

⁴⁹⁴ R. Heck, J. Corse, E. Grunwald, and S. Winstein, *J. Amer. Chem. Soc.* **79**, 3278 (1957).

⁴⁹⁵ C. O. Guss and L. H. Jules, *J. Amer. Chem. Soc.* **72**, 3462 (1950).

⁴⁹⁶ P. Cagniant, P. Faller, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 1938 (1961).

⁴⁹⁷ P. Cagniant and D. Cagniant, unpublished work.

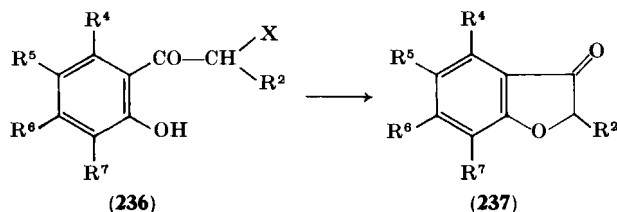
⁴⁹⁸ C. O. Guss, R. Rosenthal, and R. F. Brown, *J. Amer. Chem. Soc.* **75**, 2393 (1953).

⁴⁹⁹ C. O. Guss, *J. Amer. Chem. Soc.* **73**, 608 (1951).

⁵⁰⁰ F. Scheinmann and H. Suschitzky, *Tetrahedron* **7**, 31 (1959).

⁵⁰¹ R. Riemschneider and D. Lange, *Chem. Ber.* **97**, 300 (1964).

g. *Heterocyclic Ring Closure of o-Haloacyl Phenols: 3(2H)-Benzofuranones.* This heterocyclic ring closure of compounds **236** is an application of the von Auwers-Pohl reaction (1914). The method is frequently used for the preparation of 3(2H)-benzofuranones (**237**) (Table VII), as intermediate compounds for the synthesis of natural substances.



o-Haloacyl phenols (**236**) are usually obtained from a phenol [either by the Hoesch reaction (treatment with $\text{R}-\text{CHCl}-\text{CN}$) or by Fries rearrangement (treatment with chloroacetyl chloride, then by AlCl_3 in nitrobenzene)], or from an *o*-hydroxyacetophenone, notably by means of cuprous bromide in dioxan.⁵⁰² Heterocyclic ring closure is achieved by heating alone^{505,506} (heterocyclic ring closure can occur during preparation of **236**) with sodium acetate in ethanol, with dilute alkali,^{503,504,511,516,518,524,529} with silver acetate in toluene or in acetic

⁵⁰² K. B. Doifade and M. G. Marathe, *J. Org. Chem.* **29**, 2025 (1964).

⁵⁰³ J. N. Chatterjea, S. N. P. Gupta, and V. N. Mehrota, *J. Indian Chem. Soc.* **42**, 205 (1965).

⁵⁰⁴ J. N. Chatterjea and V. H. Mehrota, *J. Indian Chem. Soc.* **40**, 203 (1963).

⁵⁰⁵ R. Kuhn and H. A. Staab, *Chem. Ber.* **87**, 266 (1954).

⁵⁰⁶ J. P. Brown and E. B. McCall, *J. Chem. Soc.*, 3875 (1957).

⁵⁰⁷ A. K. Jaeggi and V. Renner (Geigy AG), German Offen, 1,945,161 (1970); *Chem. Abstr.* **72**, 121352 (1970).

⁵⁰⁸ R. Kuhn and H. R. Hensel, *Chem. Ber.* **84**, 557 (1951).

⁵⁰⁹ J. A. Carbon and L. S. Fosdick, *J. Amer. Chem. Soc.* **78**, 1504 (1956).

⁵¹⁰ D. Stefanye and W. L. Howard, *J. Org. Chem.* **20**, 813 (1955).

⁵¹¹ C. J. Schoot, and K. H. Klaassens, *Rec. Trav. Chim.* **75**, 190 (1956).

⁵¹² O. Dann, G. Volz, and O. Huber, *Justus Liebigs Ann. Chem.* **587**, 163 (1954).

⁵¹³ V. Arkley, F. M. Dean, A. Robertson, and P. Sidisunthorn, *J. Chem. Soc.*, 2322 (1956).

⁵¹⁴ M. C. Kloetzel, P. P. Dayton, and B. Y. Abadir, *J. Org. Chem.* **20**, 43 (1955).

⁵¹⁵ E. C. Horning and D. B. Reisner, *J. Amer. Chem. Soc.* **70**, 3619 (1948).

⁵¹⁶ G. R. Ramage and C. V. Stead, *J. Chem. Soc.*, 3602 (1953).

⁵¹⁷ S. Ebine, *Sci. Rep. Saitama Univ., Ser. A* **1**, 111 (1956); *Chem. Abstr.* **51**, 7325 (1957).

⁵¹⁸ G. Caporale and A. M. Bareggi, *Gazz. Chim. Ital.* **98**, 444 (1968).

⁵¹⁹ J. S. H. Davies, P. M. A. McCrea, W. L. Norris, and G. R. Ramage, *J. Chem. Soc.*, 3206 (1950).

⁵²⁰ K. Horvath, *Monatsh. Chem.* **82**, 901 (1951); *Chem. Abstr.* **46**, 8083 (1952).

TABLE VII

SYNTHESIS OF 3(2*H*)-BENZOFURANONES (237) FROM *o*-HALOACYL PHENOLS

Alkyl and (or) halobenzofuranones	References	Acetoxy-, hydroxy-, methoxy- benzofuranones	References
2-Me	39	5-OAc	514
5-Et	503	4-OH	532, 533
6-Et	503, 504	5-OH	532, 533
2,5-DiMe	512, 513	6-OH	515, 517, 519, 546
5-Et 2-Me	503	4,6-DiOH	524, 526, 532, 533
5-Cl	507	4,6-DiOH 2-Ph	547, 548
6-Cl	508, 509	5,6-DiOH	532, 533
5,7-DiCl	510, 511	6,7-DiOH	532-534
4,6-DiMe 5-Cl	506	6-OH 7-Me	518
		6-OH 2-Ph	547, 548
		5-Et 6-OH	517, 519-521
		5-Alkyl 6-OH	521, 522
Acyl and (or) carboxy- benzofuranones		4,6-DiOH 5-isoPr	528
2-Ac	543	5-OMe	516
2-COPh	543	6-OMe	502
2-Ac 6-OH	540	5,6-DiOMe	523
2-Ac 6-OMe	541	4,5,7 triOMe	535
2-Ac 5,6-diOMe	544	4-OMe 6-OH	524
		4-OH 6-OMe	527
		5,7-DiMe 6-OMe	505
		4,6-DiOMe 5-Me	525
		4,6-DiOMe 7-Me	525
2-Ac 5-(2,5-dihydro-5-oxofur-3-yl)	542	4,7-DiOMe 6-OH	529, 531
5-Ac 7-COOH 4,6-diOH	538, 539	5,7-DiOMe 6-OH	530
7-COOMe 4-OMe 6-OH	518	4,6-DiOMe 5-OH	536
2-Me 4-OMe 6-OH 7-Ac	545	6-OH 5-Br	536
		4,6-DiOMe 7-Cl	537

⁵²¹ J. Murai, *Sci. Rep. Saitama Univ., Ser. A* **1**, 23 (1952); *Chem. Abstr.* **49**, 3889 (1954).

⁵²² J. Murai, *Sci. Rep. Saitama Univ., Ser. A* **1**, 153 (1954); *Chem. Abstr.* **50**, 981 (1956).

⁵²³ G. A. Jones, J. B. D. MacKenzie, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 562 (1949).

⁵²⁴ T. A. Geissman and E. Hinreiner, *J. Amer. Chem. Soc.* **73**, 782 (1951).

⁵²⁵ T. C. Mulholland and G. Ward, *J. Chem. Soc.*, 1642 (1953).

⁵²⁶ J. S. H. Davies and W. L. Norris, *J. Chem. Soc.*, 3195 (1950).

⁵²⁷ L. A. Ducanson, J. F. Grove, J. MacMillan, and T. P. C. Mulholland, *J. Chem. Soc.*, 3555 (1957).

⁵²⁸ W. Bencze, J. Eisenbeis, and H. Schmid, *Helv. Chem. Acta* **39**, 923 (1956).

⁵²⁹ O. Dann and G. Illing, *Justus Liebigs Ann. Chem.* **605**, 146 (1957).

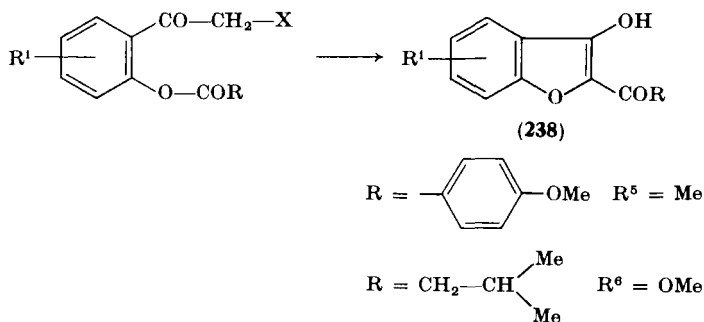
acid⁵¹⁴ or by the action of NaHCO_3 in DMF,³⁹ K_2CO_3 ,⁵⁴³ AlCl_3 ,⁵¹⁹ or $\text{Ac}_2\text{O} + \text{HClO}_4$.⁵⁴⁰

The method, which has seldom failed (but 2-hydroxy-3,5-dichloro- ω -bromacetophenone²⁷⁹ and 5-ethyl- ω -chlorogallacetophenone⁵²¹ did not undergo ring closure), does not seem to have been extended to alkyl radicals R^2 beyond $\text{R}^2 = \text{Me}$.

In the fused benzofuran series, the same method, applied to bromoacyl- o -hydroxycoumarins^{502,549} and bromoacyl- o -hydroxyxanthones^{321,433,550} allows the synthesis of the corresponding oxodihydrofuro derivatives. The nitrogenated analogs of compounds **237** (2,3-dihydro-3-oxofuro[2,3- b] and -furo[3,2- c] pyridines) have also been obtained.^{551,552}

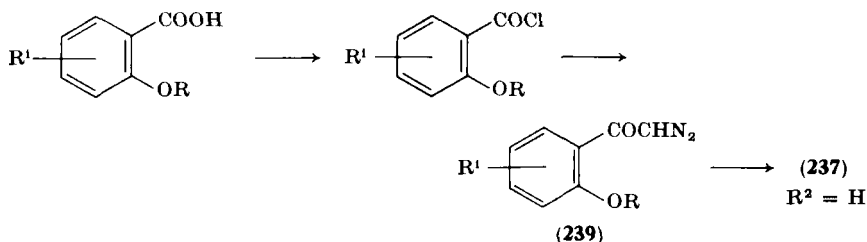
A special case, leading directly to 3-hydroxy-2-arylbenzofurans or 3-hydroxy-2-acylbenzofurans (**238**), is the ring closure (NaH) of 2-aryloxy- ω -chloroacetophenones or 2-acyloxy- ω -chloroacetophen-

- ⁵³⁰ T. A. Geissman and T. G. Halsall, *J. Amer. Chem. Soc.* **73**, 1280 (1951).
⁵³¹ Th. S. Garner, E. Wenis, and J. Lee, *J. Org. Chem.* **15**, 841 (1950).
⁵³² G. Schenck, M. Huke, and K. Goerlitzer, *Tetrahedron Lett.*, 2059 (1967).
⁵³³ G. Schenck, M. Huke, and K. Goerlitzer, *Tetrahedron Lett.*, 2375 (1968).
⁵³⁴ J. S. H. Davies and T. Deegan, *J. Chem. Soc.*, 3202 (1950).
⁵³⁵ W. J. Horton and E. G. Paul, *J. Org. Chem.* **24**, 2000 (1959).
⁵³⁶ K. J. Balakrishna, T. R. Seshadri, and G. Viswanath, *Proc. Indian Acad. Sci., Sect. A* **33**, 233 (1951); *Chem. Abstr.* **46**, 6637 (1952).
⁵³⁷ J. MacMillan, T. P. C. Mulholland, H. W. Dawkins, and K. Ward, *J. Chem. Soc.*, 429 (1954).
⁵³⁸ W. Gruber and K. Horvath, *Monatsh. Chem.* **80**, 874 (1949).
⁵³⁹ G. Caporale, *Ann. Chim. (Rome)* **48**, 650 (1958).
⁵⁴⁰ W. I. Sullivan and C. R. Hauser, *J. Org. Chem.* **25**, 839 (1960).
⁵⁴¹ S. K. Grover, V. N. Gupta, A. C. Jain, and T. R. Seshadri, *J. Sci. Ind. Res., Sect. B* **19**, 258 (1960); *Chem. Abstr.* **55**, 3066 (1961).
⁵⁴² J. Schmitt, M. Suquet, G. Callet, J. Le Meur, and P. Comoy, *Bull. Soc. Chim. Fr.*, 74 (1967).
⁵⁴³ T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.* **77**, 1623 (1955).
⁵⁴⁴ G. H. Jones, J. B. D. McKenzie, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 562 (1949).
⁵⁴⁵ A. Kagura and T. Kubota, *J. Inst. Polytech. Osaka City Univ. Ser C* **2**, 76 (1952); *Chem. Abstr.* **47**, 10526 (1953).
⁵⁴⁶ K. J. Balakrishna, N. P. Rao, and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A* **29**, 394 (1949).
⁵⁴⁷ C. Katamna, French Patent 1,502,727 (1967); *Chem. Abstr.* **69**, 964472 (1968).
⁵⁴⁸ M. A. Auger, C. Katamna, and J. Chopin, *Bull. Soc. Chim. Fr.*, 4024 (1970).
⁵⁴⁹ J. S. McIntyre (Dow. Chem. Co.), U.S. Patent 3,462,458 (1969); *Chem. Abstr.* **71**, 11290 (1969).
⁵⁵⁰ J. S. A. Davies, F. Scheinman, and H. Suschitzky, *J. Chem. Soc.*, 2140 (1956).
⁵⁵¹ H. Sliwa, *Bull. Soc. Chim. Fr.*, 646 (1970).
⁵⁵² C. Lhommet, H. Sliwa, and P. Maitte, *Bull. Soc. Chim. Fr.*, 1442 (1972).



ones,⁵⁵³ where an intramolecular transacylation (cf. Baker-Venkataraman synthesis) occurs.

h. *Heterocyclic Ring Closure of o-Alkoxy- ω -diazooacetophenones: 3(2H)-Benzofuranones.* A method related to the foregoing one provides a route to 3(2H)-benzofuranones (**237**), from diazoketones (**239**), prepared from suitable salicylic acids. Heterocyclic ring closure occurs either spontaneously^{554,555} or by treatment with an acid.^{503,556-559} The use of diazoethane leads to the methyl derivatives (**237**, R² = Me).⁵⁵⁹



o,o'-Dihydroxylated bisdiazoketones lead to furobenzofurans (**240**),⁵⁵⁹ and 2,3-dihydronaphtho[1,2-*b*]furan-3-one (**241**) has been prepared from the corresponding hydroxynaphthoic acid.^{560,561}

⁵⁵³ P. Nordsroms, (Aktiobolag. Hassle Apotekore), Netherlands Appl. 6,413,996 (1965); *Chem. Abstr.* **63**, 18043 (1965).

⁵⁵⁴ V. S. Seth and S. S. Deshapandra, *J. Indian Chem. Soc.* **27**, 429 (1950).

⁵⁵⁵ P. Pfeiffer and E. Enders, *Chem. Ber.* **84**, 247 (1951).

⁵⁵⁶ A. K. Bose and P. Yates, *J. Amer. Chem. Soc.* **74**, 470 (1952).

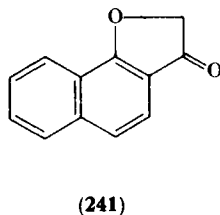
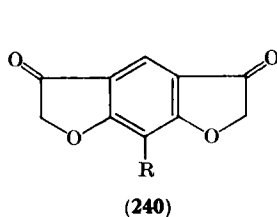
⁵⁵⁷ N. Palit and J. N. Chatterjea, *Sci. Cult.* **17**, 345 (1962).

⁵⁵⁸ H. Richtzenhain and B. Alfredsson, *Chem. Ber.* **89**, 378 (1956).

⁵⁵⁹ F. Dallacker and W. Korb, *Justus Liebigs Ann. Chem.* **694**, 98 (1966).

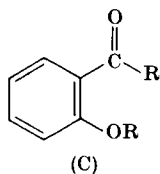
⁵⁶⁰ N. Anand and V. Venkataraman, *Proc. Indian Acad. Sci., Sect. A* **28**, 160 (1948).

⁵⁶¹ J. N. Chatterjea, *J. Indian Chem. Soc.* **31**, 194 (1954).



4. Ring Closure of *o*-Carbonylated Phenols or Phenol Ethers with Reactive Methylene Groups

In syntheses of this group, the starting material is of type C.



a. *Rössing's Method* ("Decarboxylative Cyclization"): *Ring Closure of o-Carbonylated α -Aryloxyalkanoic Acids (or Esters)*. Condensation of an α -halogenated ester with an *o*-hydroxylated carbonyl compound (242) leads readily to esters (243) or acids (244).

The acids (244) on heating at 165°–170° in the presence of acetic anhydride and sodium acetate undergo decarboxylation and ring closure (the intermediate compound 245 being isolated or not according to the conditions) to benzofuran (246,⁵⁶² $R^2 = R$).

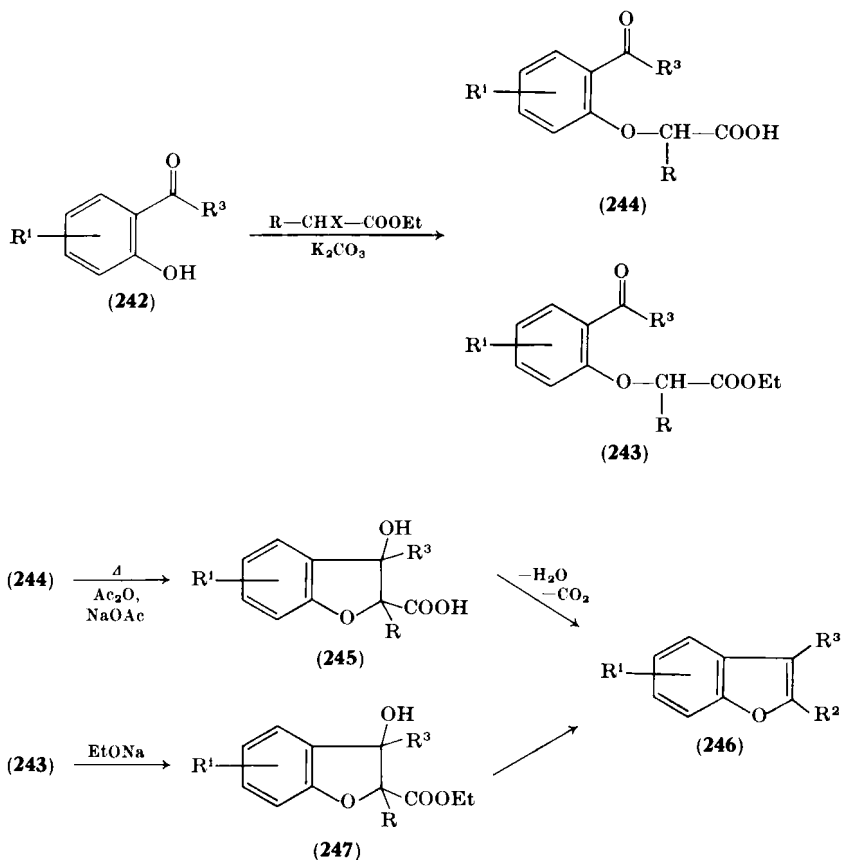
The esters (243) on treatment with sodium ethoxide in ethanol give the coumarilic ester if $R = R^3 = H$ (246, $R^2 = COOEt$).⁵⁶³ If $R, R^3 \neq H$, the intermediate compound 247 is isolated. A variant (KOH with or without water at the end of the reaction) provides the acid 246 ($R^2 = COOH$).³⁴

According to the initial aryloxyalkanoic acids used, numerous benzofurans with various substituents have been prepared in this way.

o-Formylphenoxyacetic acids (244, $R^2 = R^3 = H$) give benzofurans unsubstituted on the furan ring (Table VIII), which are intermediates in the synthesis of numerous natural substances. *o*-Acylphenoxyacetic acids (244, $R = H, R^3 = \text{alkyl}$) yield 3-alkylbenzofurans (Table IX).

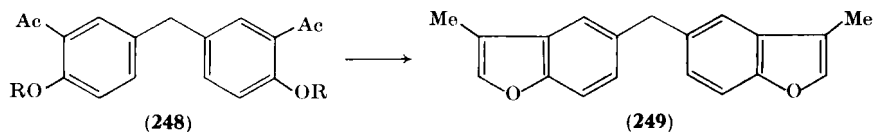
⁵⁶² A. W. Burgstahler and L. R. Worden, *Org. Syn.* **46**, 28 (1966).

⁵⁶³ M. Miyano, S. Muraki, T. Nishikubo, and M. Matsui, *Nippon Nogei Kagaku Kaishi* **34**, 678 (1960).



The diphenylmethane derivative **248** gives by double Rössing reactions the benzofurans **249**⁵⁷⁹ (R = CH₂COOEt).

Ring closure of 2-arylphenoxyacetic acids (**244**, R = H, R³ = aryl) is an unambiguous synthesis of 3-arylbenzofurans. A suitably *o*-hydroxylated benzophenone is condensed with ethyl bromoacetate;



⁵⁶⁴ W. B. Whalley, *J. Chem. Soc.*, 3481 (1953).

⁵⁶⁵ R. H. Baxter, G. R. Ramage, and J. A. Timson, *J. Chem. Soc.*, 32 (1949).

⁵⁶⁶ R. H. Baxter, G. R. Ramage, and J. A. Timson, British Patent 663,369 (1951); *Chem. Abstr.* **47**, 47754 (1953).

TABLE VIII
 BENZOFURANS FROM *o*-FORMYLPHENOXYACETIC
 ACIDS (244) R = R³ = H (or R = COOH R³ = H)

Benzofurans	Method ^a	References
5-OMe	1	564
7-OMe	1	564
5,6-DiOMe	1	564
6-OCH ₂ COOH	2	571
6-OCH ₂ Ph	2	519
2-COOMe 6-OCH ₂ Ph	2	519
5-OCH ₂ Ph 4,7-diOMe	1	565
6-OCH ₂ Ph 4,7-diOMe	1	565, 566
2-COOH 6-OH 4,7-diOMe		529
6-NO ₂ 7-OMe	2	567
2-COOH 5-Br 7-OMe	2	568, 569
4,6-diMe		570
2-COOH 4,6 diMe		570

^a Method 1: from acids (244); method 2: from esters (243).

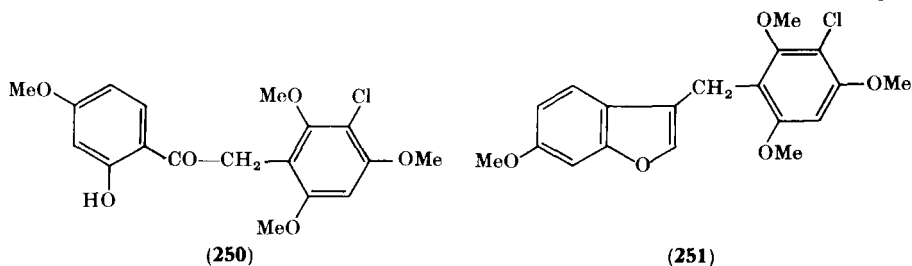
TABLE IX
 BENZOFURANS FROM *o*-ACYLPHENOXYACETIC ACIDS (244)
 R = H R³ = ALKYL

Benzofuran (246)	Method ^a	References
3-Me 4-OH	1	572
3-Me 5-OMe	1	564
3-Me 7-OMe	1	564
3-Me Bz-methyl (or dimethyl)	1	216
3,6-DiMe	2	216
3,4,6-TriMe	1	570
3,5,6-TriMe	1	573
3-Me 5-OMe	1	574
3-Me 6-OMe	2	575
3-Me 5,6-methylene dioxy	1	174
3-Me halogenated on homocycle	1	224
3-Me 6-OMe 7-Cl (or I)	2	568, 574
3-Me 4-OMe 5-I	2	568, 574
3-Et 4,6-diMe	1	570
3-Et 5,6-diOMe	1	334
3-Et 5-Cl 6-Me	1	576
3-Pr various	1	574, 577
3-Alkyls (R ³ = Me, Et, Pr, Bu)	1	578

^a Method 1: from acids (244); method 2: from esters (243).

hydrolysis gives an acid (**244**, $R = H$, $R^3 = \text{aryl}$), which leads to the corresponding benzofuran.⁵⁸⁰⁻⁵⁸³ Depending on the substituents, the benzophenone (3-Cl 6-OH) can lead directly to **247**, $R = H$, $R^3 = \text{Ph}$, $R^5 = \text{Cl}$), then to **246** ($R^2 = \text{COOEt}$, $R^3 = \text{Ph}$, $R^5 = \text{Cl}$).⁵⁸²

The same sequence of reactions from *o*-hydroxylated deoxybenzoins (**250**) forms 3-benzylbenzofurans, e.g., **251**.⁵⁸⁴ Similarly, *o*-hydroxylated benzils with suitable α -bromoalkanoic esters give 3-benzoylbenzofurans^{397,585} (e.g., **253**, $R = H$).⁵⁸⁶ When $R = \text{OMe}$, the resulting



⁵⁸⁷ F. Bordin, R. Bevilacqua, and F. Dabbeni-Sala, *Gazz. Chim. Ital.* **99**, 1177 (1969).

⁵⁸⁸ V. S. Salvi and S. Sethna, *J. Indian Chem. Soc.* **45**, 433 (1968); *Chem. Abstr.* **69**, 106, 375 (1968).

⁵⁸⁹ L. R. Worden, K. D. Kaufman, J. A. Weiss, and T. K. Schaaf, *J. Org. Chem.* **34**, 2311 (1969).

⁵⁹⁰ F. M. Dean, P. Halewood, S. Mongkolsuk, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1251 (1953).

⁵⁹¹ L. R. Worden, A. W. Burgstahler, K. D. Kaufman, J. A. Weiss, and T. Schaaf, *J. Heterocycl. Chem.* **6**, 191 (1969).

⁵⁹² W. B. Whalley, *J. Chem. Soc.*, 3229 (1951).

⁵⁹³ R. Royer, L. René, R. Cavier, and P. Barbier, German Offen. 2,113,489 (1970); *Chem. Abstr.* **76**, 366 (1972).

⁵⁹⁴ T. Abe and T. Shimizu, *Nippon Kagaku Zasshi* **91**, 753 (1970).

⁵⁹⁵ H. Dewein, *Seifen, Ole, Fette, Wachse* **19**, 117 (1955).

⁵⁹⁶ D. S. Deorha, and P. Gupta, *J. Indian Chem. Soc.* **41**, 371 (1964).

⁵⁹⁷ F. M. Dean, D. S. Deorha, J. C. Knight, and T. Francis, *J. Chem. Soc.*, 3271 (1961).

⁵⁹⁸ G. Rosseels, J. Matteazzi, M. Claret, and M. Prost, *Lab. Labaz Ing. Chim. (Brussel)* **53**, 37 (1971); *Chem. Abstr.* **77**, 5258 (1972).

⁵⁹⁹ S. P. Prajapati and S. Sethna, *J. Indian Chem. Soc.* **49**, 391 (1972).

⁶⁰⁰ P. C. Johnson and A. Robertson, *J. Chem. Soc.*, 2381 (1950).

⁶⁰¹ J. N. Chatterjea, P. Bannerji, and N. M. Sahay, *J. Indian Chem. Soc.* **45**, 171 (1968); *Chem. Abstr.* **69**, 59015 (1968).

⁶⁰² G. N. Walker and R. J. Smith, *J. Org. Chem.* **36**, 305 (1971).

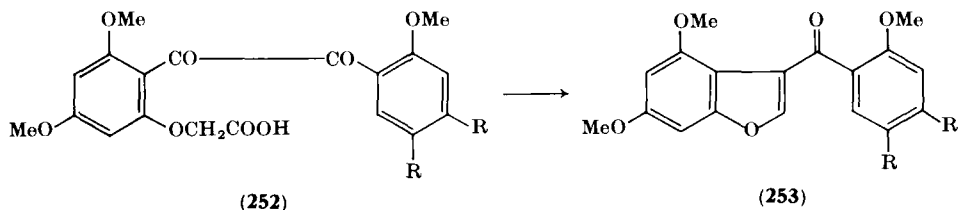
⁶⁰³ J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.* **34**, 155 (1957).

⁶⁰⁴ G. Lloyd and W. B. Whalley, *J. Chem. Soc.*, 3209 (1956).

⁶⁰⁵ R. H. Mehta, *Indian J. Chem.* **3**, 574 (1965).

⁶⁰⁶ C. A. Anirudhan, W. B. Whalley, and M. M. E. Badran, *J. Chem. Soc. C*, 629 (1966).

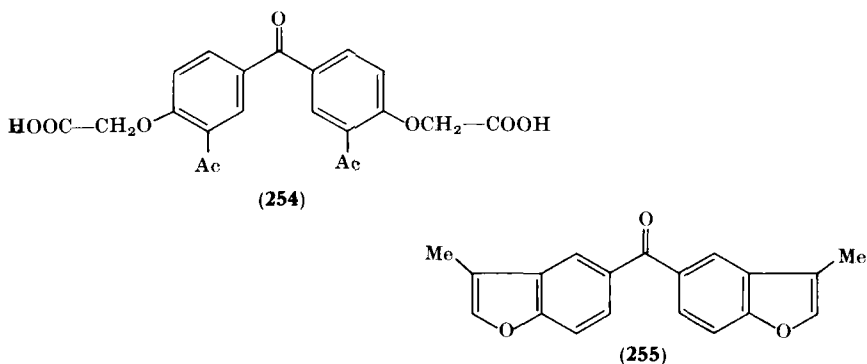
compound is not a benzofuran (**253**, R = OMe), but the isoflavonoid isomer. Substituted *o*-formyl-(or *o*-acyl-)aryloxyacetic acids (**244**, R = alkyl, R³ = H or alkyl) lead to 2,3-dialkylbenzofurans.^{334,574} If R = aryl, 2-arylbenzofurans are obtained^{40,236,239,587-591} (Kawai reaction, 1939).



The intermediate compounds **245** (R = Ph), **247** (R = Ph),⁵⁸⁹ and **247** (R = PhCH₂OC₆H₄)⁵⁹² can be isolated. They are readily converted (30% H₂SO₄, 2 hours reflux) into the corresponding 2-arylbenzofurans.

4-Methoxylated *o*-hydroxypropiophenones and *o*-hydroxybutyrophenones fail to give the corresponding 2-phenyl-3-ethylbenzofurans and 2-phenyl-3-propylbenzofurans.²³⁶

A double Rössing reaction can be achieved from benzophenone (**254**), giving bis-(3-methyl-5-benzofuranyl) ketone (**255**).^{592a}



⁵⁸⁷ A. S. Angeloni, F. Delmoro, and M. Tramontini, *Ann. Chim. (Rome)* **53**, 1151 (1963).

⁵⁸⁸ A. S. Angeloni, F. Delmoro, and M. Tramontini, *Bol. Sci. Fac. Chim. Ind. Bologna* **21**, 243 (1963); *Chem. Abstr.* **60**, 15808 (1964).

⁵⁸⁹ A. S. Angeloni and M. Tramontini, *Bol. Sci. Fac. Chim. Ind. Bologna* **55**, 1028 (1965).

⁵⁹⁰ K. Schofield, R. S. Ward, and A. M. Choudhury, *J. Chem. Soc. C*, 2834 (1971).

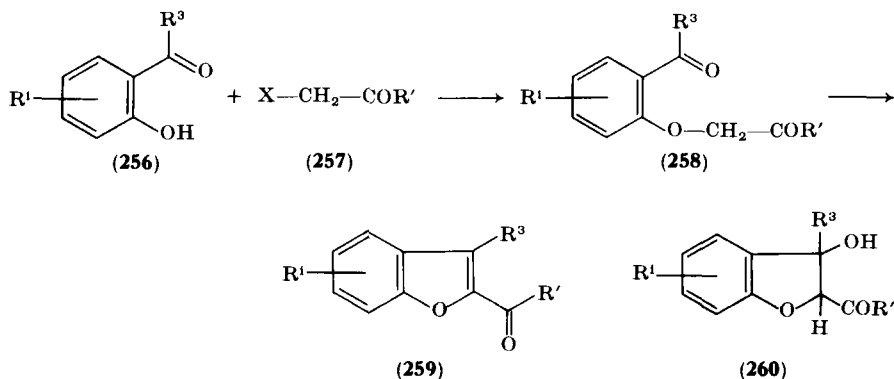
⁵⁹¹ W. Bottomley, *Chem. Ind. (London)*, 170 (1956); *Chem. Abstr.* **50**, 13894 (1956).

⁵⁹² A. F. Wagner, U.S. Patent 2,892,847 (1959); *Chem. Abstr.* **54**, 570 (1960).

^{592a} R. A. Balani and S. Sethna, *J. Indian Chem. Soc.* **45**, 390 (1968); *Chem. Abstr.* **70**, 3452 (1969).

The Rössing's method allows the synthesis of numerous polycyclic benzofurans: naphtho[2,3-*b*]furan,^{593,594} naphtho[2,1-*b*]furan,⁵⁹⁵ naphtho[1,2-*b*]furan⁵⁹⁵ and its methoxy⁵⁹⁵ and 3-(1-naphthyl)^{595a} derivatives, acenaphtho[5,4-*b*]furans;⁵⁹⁶ anthro[2,1-*b*]furans;⁵⁹⁷ phenanthro[2,1-*b*]furans;⁵⁹⁸ furo[2,3-*f*]benzofurans;^{569,599} furochromones;^{600,601} furocoumarins, such as 3,9-dimethylpsoralene,⁵⁸⁵ 3-methylxanthotoxin,⁵⁹⁴ 4,9-dimethylxanthotoxin,⁶⁰¹ 4-methylangelicin, and 4,9-dimethyl angelicin,^{602,603} and others,⁶⁰⁴ furoflavones and furoisoflavones;^{33,605} linear^{606,607} and angular^{608,609} furoxanthones; benzo[*a*]furo[2,3-*h*]xanthones and benzo[*a*]furo[2,3-*i*]xanthones.⁶¹⁰ The method failed in the furoquinoline series.⁶¹¹

b. *The Rap* (1895), *Stoermer* (1901), and *Schaeffer* (1903) *Methods*. These methods consist in condensing an *o*-hydroxylated aromatic carbonyl compound with an α -halogenated carbonyl compound. Intramolecular aldolization followed by dehydration gives benzofuran (259), the intermediate compound 260 is isolated in some cases.^{612,613} Condensation is catalyzed by anhydrous K_2CO_3 in acetone,^{614,615} methyl ethyl ketone, or DMF^{616,617} or by anhydrous KOH in ethanol.⁶¹⁸⁻⁶²⁰



⁵⁹³ K. Takeda, T. Shimada, and K. Kitanaki, *J. Pharm. Soc. Jap.* **70**, 268 (1950); *Chem. Abstr.* **45**, 1574 (1951).

⁵⁹⁴ C. Antonello, *Gazz. Chim. Ital.* **88**, 415 (1958).

⁵⁹⁵ P. Emmott and R. Livingstone, *J. Chem. Soc.*, 3144 (1957).

^{595a} J. N. Chatterjea and K. D. Banerji, *J. Indian Chem. Soc.* **47**, 576 (1970).

⁵⁹⁶ T. C. Thomas and S. Sethna, *J. Indian Chem. Soc.* **44**, 334 (1967).

⁵⁹⁷ N. N. Shah and S. Sethna, *J. Org. Chem.* **24**, 1783 (1959).

⁵⁹⁸ T. Zawadowski, *Roczn. Chem.* **44**, 151 (1970); *Chem. Abstr.* **73**, 25212 (1970).

⁵⁹⁹ C. Musante, *Gazz. Chim. Ital.* **87**, 470 (1957).

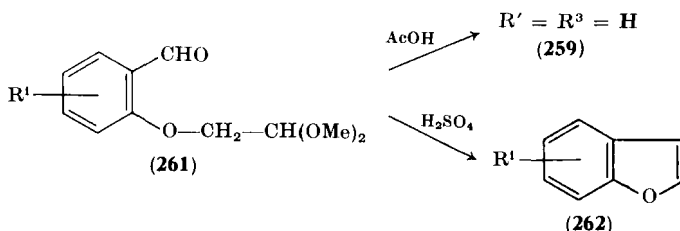
⁶⁰⁰ U. V. S. Murti and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A*, 107 (1949).

⁶⁰¹ U. V. S. Murti and T. R. Seshadri, *J. Sci. Ind. Res.* **88**, 112 (1949); *Chem. Abstr.* **44**, 5875 (1950).

⁶⁰² C. Antonello, *Gazz. Chim. Ital.* **88**, 430 (1958).

i. *Condensation of o-hydroxylated aromatic aldehydes (256, $R^3 = H$) with an α -halogenated aldehyde (257, $R' = H$) or its dimethyl acetal: 2-formylbenzofurans.* The simplest instance is the condensation of salicylaldehyde with chloro(or bromo)acetaldehyde (257, $R' = H$) to 2-formylbenzofuran (259, $R^1 = R^3 = R' = H$)⁶²¹ (Table X).

The same reaction can be effected from the dimethyl acetal of aldehyde 257: ring closure of the intermediate compound 261 by means of an organic acid⁶²¹ (AcOH) gives the corresponding 2-formylbenzofuran (259). In the presence of an inorganic acid⁶²¹ (boiling 20% H_2SO_4), the benzofuran 262 is obtained directly: in some instances, this is one of the neatest syntheses of such compounds.



ii. *Condensation of o-hydroxylated aromatic aldehydes (256, $R_3 = H$) with α -halogenated aliphatic ketones: 2-acylbenzofurans.* Condensation of

⁶⁰³ Z. Kubaj, *Roczn. Chem.* **42**, 675 (1968).

⁶⁰⁴ R. H. Mehta and S. Sethna, *J. Indian Chem. Soc.* **40**, 384 (1963).

⁶⁰⁵ L. Ramachandran Row and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A* **33**, 168 (1951).

⁶⁰⁶ Y. A. Agasimundin and S. Rajagopal, *Chem. Ber.* **100**, 383 (1967).

⁶⁰⁷ Y. S. Agasimundin and S. Rajagopal, *J. Org. Chem.* **36**, 845 (1971).

⁶⁰⁸ Y. S. Agasimundin and S. Rajagopal, *Chem. Ber.* **98**, 1910 (1965).

⁶⁰⁹ Ch. S. Angadiyavar and S. Rajagopal, *Indian J. Chem.* **7**, 1088 (1969).

⁶¹⁰ A. N. Goud and S. Rajagopal, *Monatsh. Chem.* **99**, 1100 (1968).

⁶¹¹ R. J. Chudgar and K. N. Trivedi, *J. Indian Chem. Soc.* **48**, 739 (1971).

⁶¹² M. Ghelardoni, V. Pestellini, and C. Musante, *Gazz. Chim. Ital.* **99**, 1273 (1969).

⁶¹³ A. B. Sen and M. S. Saxena, *J. Indian Chem. Soc.* **36**, 283 (1959); *Chem. Abstr.* **54**, 9875 (1960).

⁶¹⁴ E. D. Elliott, *J. Amer. Chem. Soc.* **73**, 754 (1951).

⁶¹⁵ E. Bisagni, N. P. Buu-Hoi, and R. Royer, *J. Chem. Soc.*, 3688 (1955).

⁶¹⁶ J. D. Brewer and J. A. Elix, *Tetrahedron Lett.*, 4139 (1969).

⁶¹⁷ J. D. Brewer and J. A. Elix, *Aust. J. Chem.* **25**, 545 (1972).

⁶¹⁸ Société Labaz, Belgian Patent 553,621 (1957); *Chem. Abstr.* **53**, 22016 (1959).

⁶¹⁹ N. P. Buu-Hoi and C. Beaudet, U.S. Patent 3,012,042 (1961); *Chem. Abstr.* **57**, 11168 (1962).

⁶²⁰ M. Ghelardoni, F. Russo, and V. Pestellini, *Bol. Chim. Farm.* **109**, 48 (1970); *Chem. Abstr.* **73**, 14594 (1970).

⁶²¹ M. Descamps and F. Henaux (Soc. Belge de l'azote), French Patent 1,537,206 (1968); *Chem. Abstr.* **71**, 61198 (1969).

TABLE X
2-FORMYLBENZOFURANS (AND BENZOFURANS) FROM *o*-HYDROXY
AROMATIC ALDEHYDES AND α -HALOALDEHYDES

Benzofuran	References
4-Me 6-OMe 2-CHO	616, 617
5-Cl 2-CHO (or 5-Cl)	621
5,7-DiCl 2-CHO (or 5,7-diCl)	621
5-Br 2-CHO (or 5-Br)	621
5,7-DiBr 2-CHO (or 5,7-diBr)	621
5-NO ₂ 2-CHO (or 5-NO ₂)	621
5-OMe 2-CHO (or 5-OMe)	621
5-Piperidinomethyl 2-CHO (or 5-piperidinomethyl)	621

salicylaldehyde with chloroacetone (K₂CO₃ in acetone) or chloromethyl ethyl ketone (KOH in dilute alcohol) gives 2-acetylbenzofuran^{614,615} and 2-propionylbenzofuran,^{618,619} respectively. Extension of the reaction to other α -halogenated ketones does not seem to have been attempted. The yield of the reaction has been incorrectly reported as low⁶²² (Table XI).

TABLE XI
2-ACYLBENZOFURANS FROM *o*-HYDROXY
AROMATIC ALDEHYDES AND
 α -HALOKETONES

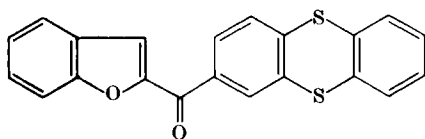
Benzofuran	References
2-Ac	614, 615
2-Ac 6-PhCH ₂ O	623
2-Ac 6-OMe	624
2-Ac 5-Me 7-OMe	625
2-Ac 5,6-methylenedioxy	174
2-Ac 5-Me	625
2-Ac 7-allyl	626
2-Ac 5-Me 7-allyl	626
2-Ac 5-NO ₂	216
2-Ac 5-Cl	615
2-Ac 7-OMe	399
2-Ac 5- <i>p</i> -ClC ₆ H ₄ CH ₂	627
2-Ac 5-COOMe 4-OH	628
2-COEt	618, 619

⁶²² N. P. Buu-Hoi, N. D. Xuong, and N. V. Bac, *J. Chem. Soc.*, 173 (1964).

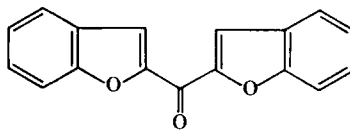
iii. *Condensation of o-hydroxylated aromatic aldehydes (256, $R_3 = H$) with aromatic haloketones ($X-CH_2-COAr$): 2-aroylebenzofuranes (259, $R_3 = H, R' = Ar$). 2-Aroylebenzofurans (259, $R_3 = H, R' = At$) can be obtained in outstanding yields (80–100%) from salicylaldehydes with various substituents and phenacyl bromide (K_2CO_3 in acetone) or other aromatic haloketones with various substituents (257, $R' = Ar$) (Table XII).*

In the case where $R_1 = R_3 = H, R' = p-XC_6H_4$, with $X = F, Cl, Br$, the intermediate compound (260) has been isolated as the *cis* and *trans* stereoisomers^{612,620} and readily converted into the corresponding benzofuran.

The use of complex aromatic α -haloketones affords special 2-aroylebenzofurans, such as 263 (condensation of salicylaldehyde with 2-bromoacetylthianthrene)⁶³⁴ and 264 (condensation of salicylaldehyde with 2-bromoacetylbenzofuran).³⁹⁹



(263)



(264)

iv. *Condensation of o-hydroxylated aromatic aldehydes with compounds of general structure $X-CH_2-Y$ ($X = \text{halogens}$). This method leads to 5-, 6-, and 7-substituted benzofurans 2-substituted by Y (265),^{635–638} where Y is NO_2 ,^{639,640} $CONH_2$,⁶⁴¹ CN ,⁶⁴¹ $p-O_2NC_6H_4$.^{635–638}*

⁶²³ J. B. D. MacKenzie, A. Robertson, A. Bushra, and R. Towers, *J. Chem. Soc.*, 2061 (1949).

⁶²⁴ J. A. Elix, *Aust. J. Chem.* **24**, 93 (1971).

⁶²⁵ R. Royer, G. Menichi, J. P. Buisson, M. Hubert Habart, and M. Cheutin, *Bull. Soc. Chim. Fr.*, 2405 (1967).

⁶²⁶ J. M. Osborn, G. H. Fothergill, and J. C. Wickers (Roche Ltd.), British Patent 1,106,058 (1968); *Chem. Abstr.* **69**, 35922 (1968).

⁶²⁷ N. P. Buu-Hoi, T. B. Loc, and N. D. Xuong, *J. Org. Chem.* **21**, 1438 (1956).

⁶²⁸ M. Miyano and M. Matsui, *Chem. Ber.* **93**, 54 (1960).

⁶²⁹ M. W. Ruchelman, Ph. D. Thesis, Univ. of Houston, Texas, 1963.

⁶³⁰ E. Merck, A. G., Netherlands Patent Appl. 6,602,929 (1966); *Chem. Abstr.* **66**, 53370 (1967).

⁶³¹ N. P. Buu-Hoi, G. Saint-Ruf, T. B. Loc, and N. D. Xuong, *J. Chem. Soc.*, 2593 (1957).

⁶³² M. Ghelardoni, M. Fedi, and F. Russo, *Ann. Chim. (Rome)* **52**, 29 (1962); *Chem. Abstr.* **57**, 2165 (1962).

⁶³³ K. Weinges, Y. Naya, and F. Toribio, *Chem. Ber.* **96**, 2780 (1963).

⁶³⁴ G. Vasilu and E. Cohn, *An. Univ. Bucuresti Ser. Stiint. Nat.* **13**, 95 (1966); *Chem. Abstr.* **64**, 15873 (1966).

⁶³⁵ K. B. L. Mathur and H. S. Mehra, *J. Chem. Soc.*, 1954 (1960).

TABLE XII
2-AROYL BENZOFURANS FROM SALICYLIC ALDEHYDES
AND AROMATIC HALOKETONES

Benzofuran	References
2-COPh	629
2-COPh-5-Me	613
2-COPh 5-Cl	613
2-COPh 5-Ph	613
2-COPh 5- <i>t</i> -Bu 7Cl	613
2-COPh 6-MeO	615
2-CO (<i>p</i> -MeOC ₆ H ₄)	615
2-CO (<i>p</i> -EtOC ₆ H ₄)	507
2-CO- (<i>p</i> -O ₂ NC ₆ H ₄)	632
2-CO (<i>p</i> -FC ₆ H ₄)	612, 620
2-CO (<i>p</i> -ClC ₆ H ₄)	612, 620
2-CO (<i>p</i> -BrC ₆ H ₄)	62, 612, 620
2-CO (3,4-diMeO C ₆ H ₃)	633
2-CO (3-MeO-4-HOC ₆ H ₃)	558
2-CO (2-MeO-5-FC ₆ H ₃)	65
2-CO (3-F-4-MeOC ₆ H ₃)	65
2-CO-(2,4-diMeC ₆ H ₃)	630
2-CO (3-F-4-MeC ₆ H ₃)	62
2-CO (3-Cl-4MeOC ₆ H ₃)	62
2-CO (2-MeO-3-MeC ₆ H ₃)	62
2-CO (4-MeO-1-naphthyl)	62
2-CO (<i>p</i> -ClC ₆ H ₄) 5-Ph	613
2-CO (<i>p</i> -ClC ₆ H ₄) 5-Cl	613
2-CO (<i>p</i> -BrC ₆ H ₄) 5-Cl	631
2-CO (<i>p</i> -MeOC ₆ H ₄) 5-Cl	631
2-CO (<i>p</i> -ClC ₆ H ₄) 5-Me	613
2-CO (2,4-diMeC ₆ H ₃) 5-Cl	631
2-CO (3-Cl-4-MeOC ₆ H ₃) 5-Cl	631
2-CO (3-F-4-MeOC ₆ H ₃) 5-Br	65
2-CO (3-Cl-4-MeOC ₆ H ₃) 5-Br	631
2-CO (3-F-4-MeOC ₆ H ₃) 5,7-diCl	65
2-CO (<i>p</i> -ClC ₆ H ₄) 5- <i>t</i> -Bu 7-Cl	613
2-CO (3,4-diMeOC ₆ H ₃) 5-CHO 7-OMe	558
Others	62

⁶³⁶ A. L. Mndzhoyan and G. L. Papayan, USSR Patent 158,888 (1963); *Chem. Abstr.* **60**, 11986 (1964).

⁶³⁷ A. L. Mndzhoyan and G. L. Papayan, USSR Patent 166,042 (1964); *Chem. Abstr.* **62**, 10412 (1965).

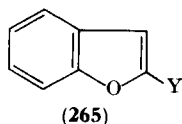
⁶³⁸ H. Singh and J. C. Verma, *J. Indian Chem. Soc.* **40**, 31 (1963).

⁶³⁹ R. Royer, P. Demerseman, and L. René, *Bull. Soc. Chim. Fr.*, 3740 (1970).

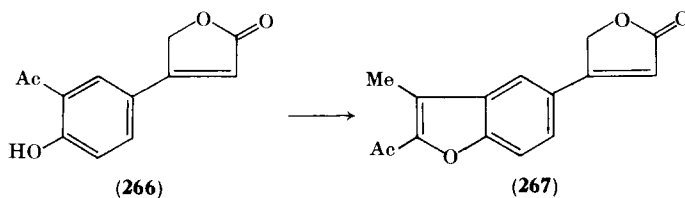
⁶⁴⁰ R. Royer, P. Demerseman, and R. Cavier (Anvar), German Offen. 2,131,927 (1972); *Chem. Abstr.* **77**, 19520 (1972).

⁶⁴¹ L. René and R. Royer, *Bull. Soc. Chim. Fr.*, 4329 (1971).

The method has been extended to *o*-hydroxylated naphthalenic and heterocyclic aldehydes, which leads to complex benzofurans, naphthofurans,^{62,65,613,615} and furocoumarins.⁵⁹⁴



v. *Condensation of o-hydroxylated aromatic ketones (256, R³ ≠ H) with α-halogenated ketones.* Although some authors⁶¹⁵ have maintained that *o*-hydroxylated aromatic ketones could not be used for the synthesis of benzofurans by condensation with chloroacetone, several instances are quoted in Table XIII. Compounds with vasodilatory properties, e.g., **267**, have thus been prepared from the ketone **266**.^{69,542,642} The



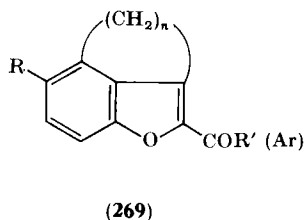
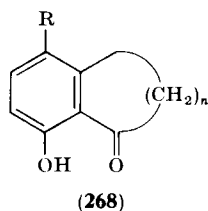
reaction has been applied to *o*-hydroxylated semiaromatic cyclic ketones (**268**), giving "bridged" benzofurans (**269**).⁶⁴³ The reaction failed for the case where $n = 2$.

TABLE XIII
BENZOFURANS FROM *o*-HYDROXY-
LATED AROMATIC KETONES
AND CHLOROACETONE

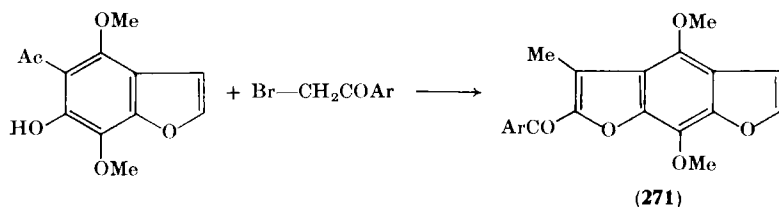
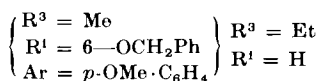
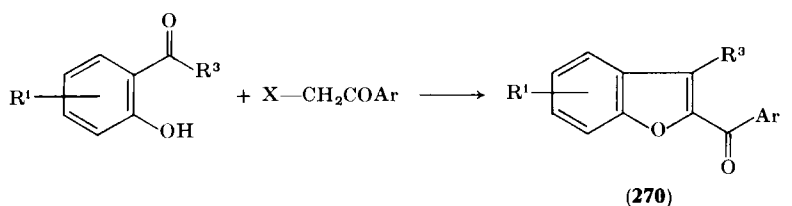
Benzofuran	References
2-Ac 3-Me 6-OMe	623
2-Ac 3,6-diMe	216
2-Ac 2,5,6-triMe	216
2-Ac 3-Me 5-OMe	10
2-Ac 3-Me 7-OMe	10
2-Ac 3-Me 6-Cl	216
2-Ac 3,6-diMe 5-Cl	224
2-Ac 3-Me 6-Cl	224

⁶⁴² J. Schmitt, M. Suquet, G. Callet, J. Le Meur, and P. Comoy, *J. Med. Besançon* 187 (1966); *Chem. Abstr.* **67**, 64145 (1967).

⁶⁴³ R. Royer, E. Bisagni, and G. Menichi, *Bull. Soc. Chim. Fr.*, 2112 (1964).



vi. *Condensation of o-hydroxylated aromatic ketones with aromatic haloketones* $X-CH_2-CO-Ar$. The reaction leads to 2-aryl-3-methylbenzofurans^{208,615} (cf. **270**)⁶²³ and to 2-aryl-3-ethylbenzofurans. 2-*p*-Anisoyl-3-methylbenzofurans and 2-*p*-anisoyl-3-ethylbenzofurans have thus been synthesized with a view to testing their estrogenic properties (Table XIV).⁶⁴⁴ The method has also been used for preparing complex benzofurans (**271**).^{52,208}



vii. *Condensation of o-hydroxylated aromatic ketones with compounds* $X-CH_2-Y$. Condensation of *o*-hydroxylated aromatic ketones has been achieved with *p*-nitrobenzyl bromide ($Y = \text{Ar}$),^{645,646} with chloroacetamide ($Y = \text{CONH}_2$),⁶⁴¹ and with chloroacetonitrile ($Y = \text{CN}$)⁶⁴¹ (giving the nitrile and the amide), but it failed with bromonitromethane ($Y = \text{NO}_2$).⁶⁴¹

⁶⁴⁴ H. Singh and R. Kapil, *J. Org. Chem.* **24**, 2064 (1959).

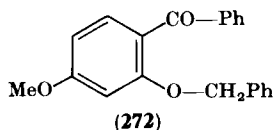
⁶⁴⁵ H. Singh and J. Ch. Verma, *J. Indian Chem. Soc.* **39**, 49 (1962).

⁶⁴⁶ D. S. Deorha and S. K. Mukerjee, *J. Indian Chem. Soc.* **40**, 817 (1963).

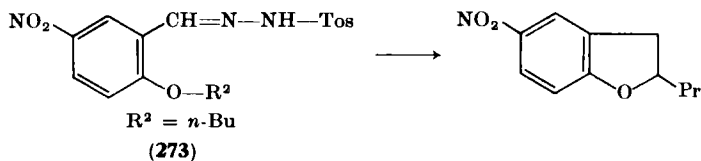
TABLE XIV
BENZOFURANS FROM *o*-HYDROXYLATED AROMATIC
KETONES AND AROMATIC HALOKETONES

Benzofuran	References
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Me 6-PhCH ₂ O	623
2- <i>p</i> -MeOC ₆ H ₄ CO 3,5-diMe	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Me 5-Cl	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Me 5-Br	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3,5-diMe 7-Br	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Me 5,6-diCl	644
2-PhCO 3-Et	615
2-(2-Me-4-MeO-5-isoPrC ₆ H ₂ CO) 3-Et	208
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Et 5-Cl	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Et 5-Br	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Et 5-Me	644
2- <i>p</i> -MeOC ₆ H ₄ CO 3-Et	615

viii. *Special instances of the Rap reaction.* Photoinduced ring closure of compound **272** gives ready access to 2,3-diphenyl-6-methoxybenzo-



furan.⁶⁴⁷ Thermal and photolytic degradation of the *p*-toluenesulfonyl-hydrazone **273** leads, via an *o*-substituted arylcarbene, to the corresponding 2,3-dihydrobenzofuran.⁶⁴⁸



c. *Condensation of Hydroxylated Aromatic Carbonyl Compounds with Ethyl Bromomalonate (Tanaka's Method).*^{649,650} This method, a variation of the Rössing reaction, allows the synthesis of benzofurans unsubstituted on the benzene ring, in 60–80% yields, and is especially

⁶⁴⁷ G. R. Lappin and J. S. Zauucci, *J. Chem. Soc.*, 1113 (1969).

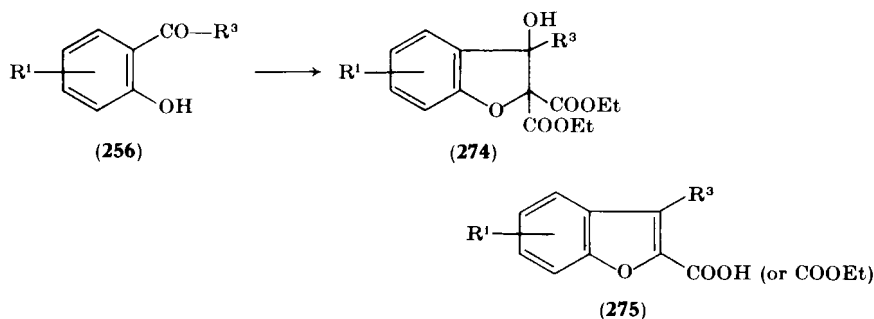
⁶⁴⁸ G. V. Garner, D. B. Mobbs, H. Suschitzky, and J. S. Millership, *J. Chem. Soc. C*, 3693 (1971).

⁶⁴⁹ S. Tanaka, *J. Amer. Chem. Soc.* **72**, 307 (1951).

⁶⁵⁰ S. Tanaka, *J. Amer. Chem. Soc.* **73**, 282 (1952).

suitable for the synthesis of natural substances. It consists in condensing *o*-hydroxyaryl aldehydes (**256**, $R_3 = H$) and *o*-hydroxyacetophenones (**256**, $R^3 = Me$) with ethyl bromomalonate in acetic acid, in the presence of K_2CO_3 . The intermediate (**274**) is not isolated. The coumarilic ester or acid (**275**) obtained is decarboxylated to the corresponding benzofuran (Table XV). The condensation product (**275**, $R_3 = Me$) from *o*-hydroxyacetophenone (38% yield) could not be decarboxylated.⁶⁴⁹

The method has been extended to *o*-hydroxyaryl ketones for the synthesis of naphtho[1,2-*b*]furanes,⁶⁵⁶ thieno[3,2-*e*]benzofurans,⁶⁵⁷ furoflavones,⁶⁵⁸ furoxanthones,⁶⁵⁹ furoquinolines,^{611,660} phenanthrofurans,⁶⁶⁰ and other complex benzofurans.⁶⁶¹



d. *Synthesis of Benzofuran Derivatives from o-Carboethoxy Aryloxyacetic Acids (or Their Esters)*. The sodium derivatives of salicylic esters are readily condensed with ethyl bromoacetate. Dieckman ring closure of the resulting esters (**276**) leads to β -ketonic esters (**277**), which are

⁶⁵¹ P. Rumpf and C. Gansser, *Helv. Chim. Acta* **37**, 435 (1954).

⁶⁵² F. E. King, J. R. Hansley, and T. J. King, *J. Chem. Soc.*, 1392 (1954).

⁶⁵³ M. Descamps, J. Van-Der-Elst, and F. Binon, *Ind. Chim. Belge*, **32** (1967); *Chem. Abstr.* **70**, 68028 (1969).

⁶⁵⁴ R. Kurdukar and N. V. Subba Rao, *Proc. Indian Acad. Sci., Sect. A* **58**, 336 (1963); *Chem. Abstr.* **60**, 11972 (1964).

⁶⁵⁵ T. Matsumoto and K. Fukui, *Bull. Chem. Soc. Jap.* **30**, 3 (1957).

⁶⁵⁶ Y. Tanaka, *Bull. Chem. Soc. Jap.* **30**, 575 (1957); *Chem. Abstr.* **52**, 6310 (1958).

⁶⁵⁷ A. Mustafa and S. M. A. D. Zayed, and A. Emran, *Justus Liebigs Ann. Chem.* **704**, 176 (1967).

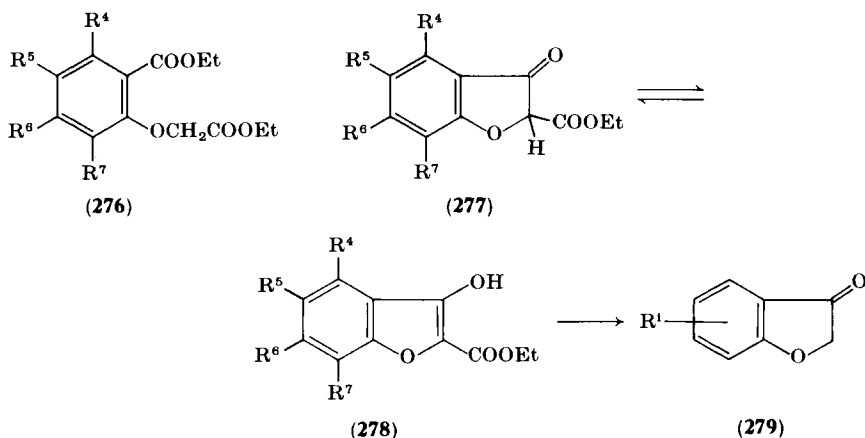
⁶⁵⁸ K. Fukui, M. Nakayama, and M. Hatanoka, *Bull. Chem. Soc. Jap.* **36**, 872 (1963).

⁶⁵⁹ G. S. Puranik and S. Rajagopal, *Indian J. Chem.* **4**, 442 (1966).

⁶⁶⁰ S. Tanaka and S. Kawai, *Nippon Kagaku Zasshi* **80**, 1183 (1959).

⁶⁶¹ Y. Kawase and C. Numoto, *Bull. Chem. Soc. Jap.* **35**, 1366 (1962).

mainly in the enolic form (**278**), stabilized by the hydrogen bond.^{662,663} Alkaline or acidic hydrolysis gives 3(2*H*)-benzofuranones (**279**) (Table XVI).



Ring closure is effected by sodium in benzene^{279,669} or dioxan,⁶⁶⁸ by EtONa in ethanol⁶⁷³ or benzene,⁶⁷⁴ or by NaH in THF;⁶⁷² the yields vary according to the substituents.⁶⁷⁴

C-alkyl derivatives (**280**) are obtained by direct addition of an alkyl halide at the end of the Dieckmann reaction, in benzene or xylene. *O*-Alkyl derivatives (**281**) are obtained by reacting sodium amide with ester **278**, previously isolated, in benzene, followed by addition of the

⁶⁶² H. Henecka, *Chem. Ber.* **81**, 179 (1948).

⁶⁶³ H. Henecka, *Chem. Ber.* **81**, 197 (1948).

⁶⁶⁴ H. I. King, R. H. Holland, F. P. Reed, and A. Robertson, *J. Chem. Soc.*, 1672 (1948).

⁶⁶⁵ V. K. Mahesh and R. K. Kela, *J. Indian Chem. Soc.* **46**, 89 (1969); *Chem. Abstr.* **70**, 114804 (1969).

⁶⁶⁶ W. U. Malik, V. K. Mahesh, and M. Raisinghani, *Indian J. Chem.* **9**, 655 (1971).

⁶⁶⁷ J. N. Chatterjea, K. Achari, and N. C. Jain, *Tetrahedron Lett.*, 3337 (1969).

⁶⁶⁸ P. D. Bartlett and E. N. Trachtenberg, *J. Amer. Chem. Soc.* **80**, 5808 (1958).

⁶⁶⁹ M. Gerecke, E. Kyburz, C. V. Planta, and A. Brossi, *Helv. Chim. Acta* **45**, 2241 (1962).

⁶⁷⁰ J. D. Brewer and J. A. Elix, *Aust. J. Chem.* **25**, 1545 (1972).

⁶⁷¹ G. M. Brooke and B. S. Furniss, *J. Chem. Soc. C*, 869 (1967).

⁶⁷² G. M. Brooke, B. S. Furniss, and W. K. R. Musgrave, British Patent 227,352 (1971); *Chem. Abstr.* **75**, 20177 (1971).

⁶⁷³ R. Tondeur, R. Sion, and E. Dcray, *Chim. Ther.* **5**, 356 (1968).

⁶⁷⁴ D. C. Schroeder, P. O. Corcoran, C. A. Holden, and M. C. Mulligan, *J. Org. Chem.* **27**, 586 (1962).

TABLE XV
BENZOFURANS FROM *o*-HYDROXYLATED
AROMATIC CARBONYL COMPOUNDS AND
ETHYL BROMOMALONATE

Benzofuran	References
5-OMe	649, 652
6-OMe	649, 652
5-NO ₂	650
7-NO ₂	650
6-NO ₂	651
6-Ph	207
5-Cl 7-NO ₂	40
5-Br 7-NO ₂	649, 652
5,6-DiOMe	649, 652
4-OH 5-COOH	655
2-COOH 3-Me	649
2-COOH 5-Me 7-piperidinomethyl	653
Miscellaneous: R ¹ = OMe	654
R ¹ = halogen	654

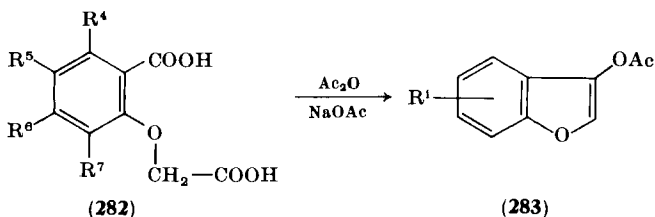
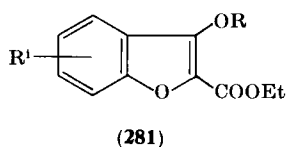
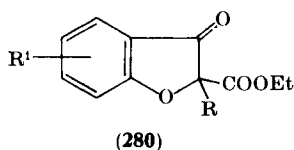
TABLE XVI
2-CARBETHOXY(OR CARBOXY)-
3-HYDROXYBENZOFURANS BY
DIECKMANN RING CLOSURE

Benzofuran (278)	References
5-Br	665, 666
7-Me	664
6-OMe	664
4-Me 6-OMe	670
5,6-DiOMe	667
3,5-DiNO ₂	668
5,7-DiCl	277
4,6-DiOMe 5-Cl	669
4,6-DiOMe 7-Cl	669
4,6-DiOMe 5,7-diCl	669
4,6-DiOMe 7-NO ₂	669
4,6-DiOMe 7-Me	669
4,6-DiOMe 7-I	669
4,5,6,7-TetraF	671, 672

alkyl halide.⁶⁷³ The influence of the conditions and substituents⁶⁷⁵⁻⁶⁷⁷ and of the solvent⁶⁶⁵ on the course (C- or O-alkylation) of the reaction has been investigated, as well as the action of benzyl chloride and *p*-nitrobenzyl chloride.⁶⁷⁸⁻⁶⁸⁰

The conversion of esters (278) to 3(2*H*)-benzofuranones (279) by hydrolysis and decarboxylation (KOH in alcohol)^{279,668,674} is sometimes difficult. Direct conversion of esters (277) into benzofurans has recently been achieved by the action of NaBH₄ on the product of the Dieckmann reaction (not isolated), followed by acidic hydrolysis (70% yield).^{681,682}

o-Carboxyaryloxyacetic acids (282) undergo direct ring closure (30-40% yields) by heating with Ac₂O + NaOAc. The 3-acetoxy derivatives (283) are readily converted into the corresponding benzofuranes.⁶⁸³ Ring closure can also be achieved thermally (282, R⁴ =



⁶⁷⁵ A. Brändström, *Ark. Kemi* **11**, 527 (1957).

⁶⁷⁶ A. Brändström and I. Forsblad, *Acta Chem. Scand.* **11**, 914 (1957).

⁶⁷⁷ I. Forsblad, *Ark. Kemi* **15**, 403 (1960).

⁶⁷⁸ N. Kornblum, *Trans. N. Y. Acad. Sci.* **29**, 1 (1966); *Chem. Abstr.* **67**, 63455 (1967).

⁶⁷⁹ N. Kornblum, R. E. Michel, and K. C. Kerber, *J. Amer. Chem. Soc.* **88**, 5660 (1966).

⁶⁸⁰ N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.* **89**, 5714 (1967).

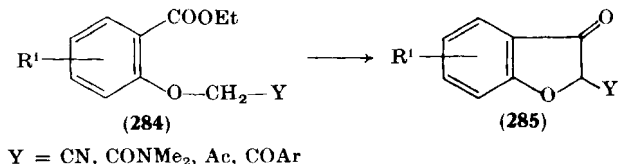
⁶⁸¹ Tran Quang Minh, L. Christiaens, and M. Renson, *Symp. Org. Sulphur Chem.* 5th 1972, IVA, 15.

⁶⁸² Tran Quang Minh, L. Christiaens, and M. Renson, *Tetrahedron* **28**, 5397 (1972).

⁶⁸³ L. Perrin and P. Cagniant, unpublished work.

$R^5 = R^7 = F$, $R^6 = OMe$).⁶⁸⁴ These various methods have also been applied to the naphthofuran series.^{283,685,686}

2-Cyano,⁶⁸⁷ 2-dimethylcarboxamido-,^{688,689} 2-acetyl-,⁵⁴³ and 2-aroyle-^{687,690} 3(2*H*)benzofuranones (285) have been obtained from the corresponding esters (284) by a similar method.



B. FUSION OF THE FURAN RING TO A NONAROMATIC CARBOCYCLE

1. General

We have gathered in this section syntheses leading to the various carbocyclic hydrogenated derivatives of benzofuran: 4,5,6,7-tetrahydrobenzofurans, 2,3,4,5,6,7-hexahydrobenzofurans and perhydrobenzofurans [the 2,3-dihydro derivatives obtained from 3(2*H*)-benzofuranones (237) are surveyed in Section IV, D, 1, a]. Those methods are treated at length, owing to the difficulty of obtaining hydrogenated derivatives from benzofuran.

2. 4,5,6,7-Tetrahydrobenzofurans

The reactions used are based mostly on the conventional ring closure of 1,4-diketones, applied to acetonyl cyclohexanones and cyclohexanediones. This leads either to 6,7-dihydro-4(5*H*)-benzofuranones, or directly to 4,5,6,7-tetrahydrobenzofurans, depending on the starting material.

⁶⁸⁴ G. M. Brooke, B. S. Furniss, and W. K. R. Musgrave, *J. Chem. Soc. C*, 580 (1968).

⁶⁸⁵ P. Emmott and R. Livingstone, *J. Chem. Soc.*, 4629 (1958).

⁶⁸⁶ D. C. C. Smith and D. E. Steere, *J. Chem. Soc.*, 1545 (1965).

⁶⁸⁷ R. Bryant and D. L. Haslam, *J. Chem. Soc.*, 2361 (1965).

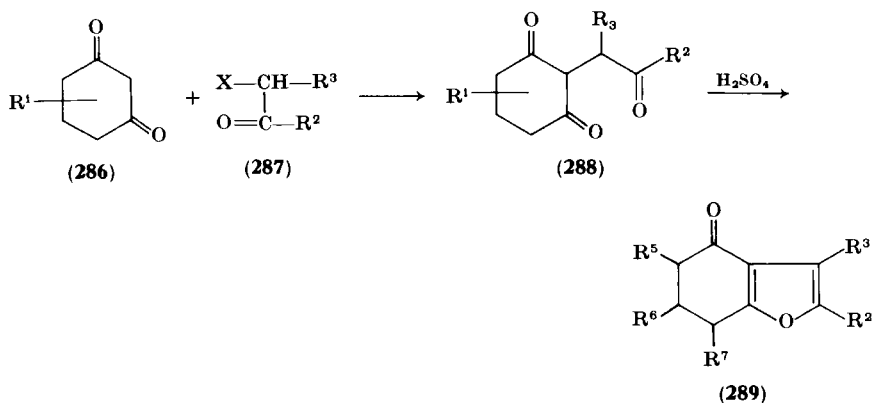
⁶⁸⁸ M. Pesson and M. Joannic, German Offen. 1,932,933 (1970); *Chem. Abstr.* **72**, 90264 (1970).

⁶⁸⁹ Laboratoires R. Bellon, French Patent 2,068,430 (1971); *Chem. Abstr.* **76**, 126769 (1972).

⁶⁹⁰ R. Bryant, *J. Chem. Soc.*, 5140 (1965).

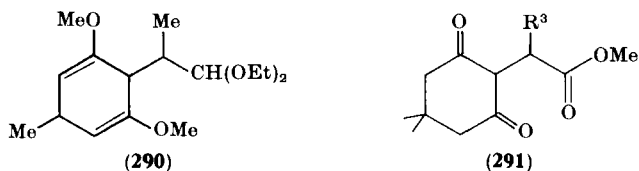
a. 6,7-Dihydro-4(5H)-benzofuranones (289)

i. Condensation of 1,3-cyclohexanediones with α -haloketones (287, $R^2 = R^3 = \text{alkyl}$, or $R^2 = \text{Ph}$, $R^3 = \text{H}$) the Stetter-Lauterbach method.^{691,692} Compounds 289 are obtained according to Scheme 5.



Condensation of diketones (286) with α -haloketones (287), in the presence of KOH-ethanol or of sodium methoxide, gives in good yield 1-acetonyl-2,6-cyclohexanediones (288). Ring closure to 6,7-dihydro-4(5H)-benzofuranones (289) is then achieved by means of H_2SO_4 or HCl (e.g., 291, $R^3 = \text{H}$ or $R^3 = \text{CH}_2\text{COOH}$)⁶⁹⁸ (Table XVII).

A variation consists in starting from dihydroresorcinol (or its dimethyl ether) and from the diacetal of compound 287: thus, evodone (289, $R^3 = R^6 = \text{CH}_3$), a natural substance, has been obtained (as the racemate) by ring closure (with HCl) of compound 290.⁶⁹³ Similarly, the



⁶⁹¹ H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.* **652**, 40 (1962).

⁶⁹² H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.* **655**, 20 (1962).

⁶⁹³ B. I. Nurunnabi, *Pakistan J. Sci. Ind. Res.* **4**, 37 (1961).

⁶⁹⁴ K. Schoen and I. J. Pachter (Endo Lab. Inc.), U.S. Patent 3,467,755 (1969); *Chem. Abstr.* **72**, 3375 (1970).

⁶⁹⁵ J. Sam and J. R. Mozingo, *J. Pharm. Sci.* **58**, 1030 (1969).

⁶⁹⁶ H. Stetter and E. Siehnhold, *Chem. Ber.* **88**, 271 (1955).

⁶⁹⁷ K. Takagi and T. Ueda, *Chem. Pharm. Bull.* **19**, 1218 (1971).

⁶⁹⁸ H. J. Schaeffer and R. Vince, *J. Org. Chem.* **27**, 4502 (1962).

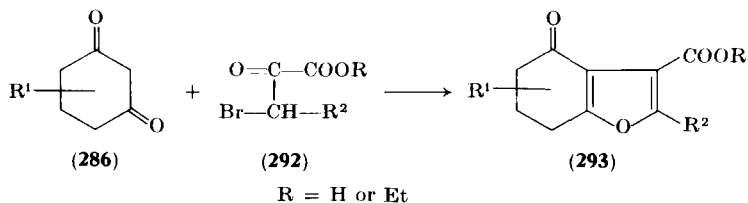
TABLE XVII
6,7-DIHYDRO-4(5*H*)-BENZOFURANONES
FROM 1,3-CYCLOHEXANEDIONES

Benzofuran (289)	References
2-Me	691
2-Et	694
2-Ph	696, 697
2,6-DiMe	691
2,3-DiMe	101
3,6-DiMe	693
5,5-DiMe	698
2-Me 3-Et	695
2,3,6-TriMe	692
2,6,6-TriMe 3-CH ₂ COOH	698
3-COOH	692
2-Me 3-COOH	699
2-COOEt 3-Me	699, 700
3-Me	699, 700
2-COOEt 3,6-diMe	699, 700
3,6-diMe	699, 700

use of phenacyl bromide (287, R² = Ph, R³ = H) leads to the corresponding compounds 288 and 289.^{696,697}

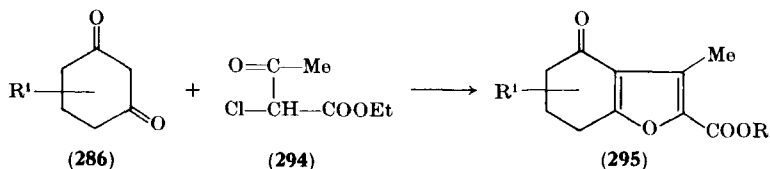
Ketone (289, R² = Ph, R³ = H) is degraded in alkaline medium to 2-phenacyl-1,3-cyclohexanedione (288, R² = Ph, R³ = H). This reaction is characteristic of a 3-acylfuran.⁶⁹⁷ Treatment of compound 288 with sulfuric acid gives back ketone (289).

ii. *Condensation of 1,3-cyclohexanediones with 3-halo-2-ketoesters (or acids)*. Diketones 286 condense with 3-halo-2-ketoesters (or acids) (292) under the same conditions as with α -haloketones affording directly 3-carboxy (or ethoxycarbonyl)-6,7-dihydro-4(5*H*)-benzofuranones (293, R³ = COOH or COOEt).^{692,699}



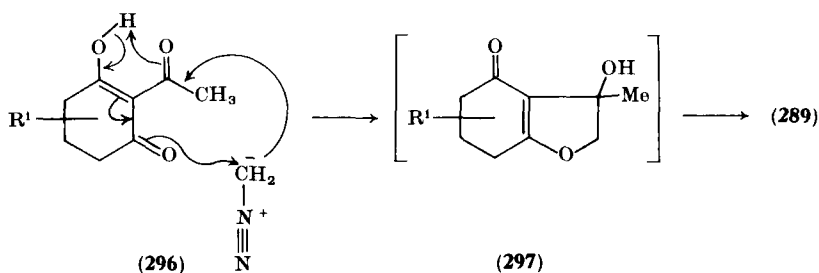
⁶⁹⁹ H. Stetter and R. Lauterbach, *Chem. Ber.* **93**, 603 (1960).

iii. *Condensation of 1,3-cyclohexanediones with ethyl α -chloroacetate* (294). This condensation leads directly to 2-carbethoxy-6,7-dihydro-4(5*H*)benzofuranones (295, R = Et). (\pm)-Evodone (289, R³ = R⁶ =

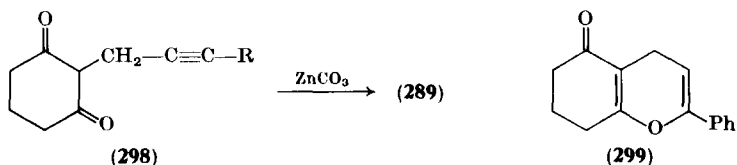


Me) (cf. Section IV, B, 2, a) has thus been synthesized by condensation of 1-methyl-3,5-cyclohexanedione with compound 294, followed by hydrolysis and decarboxylation.^{699,700}

iv. *Variations of the Stetter-Lauterbach reaction.* Reactions of diazomethane with 2-acetyl-1,3-cyclohexanediones (or 2-acetyl-3-alkoxy-cyclohexene-1-ones) afford compounds 289 (R¹ = R² = H, R³ = Me⁷⁰¹ and R³ = Me, R⁶ = Ph, R¹ = H⁷⁰²).



Ketone (289, R¹ = H) can be obtained (29% yield) by condensation of 1,3-cyclohexanedione with 1,2-dichloroethyl acetate (in the presence of ammonia),⁷⁰³ 2-propargyl-1,3-cyclohexanedione (298, R = H) [obtained from 286 (R¹ = H) and propargyl bromide], treated with ZnCO_3 ,



⁷⁰⁰ H. Stetter and R. Lauterbach, *Angew. Chem.* **71**, 673 (1959).

⁷⁰¹ G. Nowy, W. Riedl, and H. Simon, *Chem. Ber.* **99**, 2075 (1966).

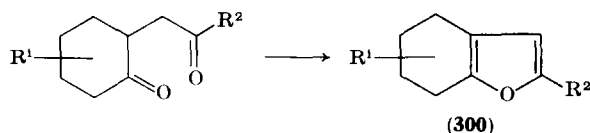
⁷⁰² A. A. Akhrem, A. M. Moisenko, F. A. Lakvich, and A. I. Poselenov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 143 (1972); *Chem. Abstr.* **77**, 34250 (1972).

⁷⁰³ E. Bisagni, J. P. Marquet, J. André, L. Fort, A. Cheutin, and F. Feinte, *Bull. Soc. Chim. Fr.*, 2796 (1967).

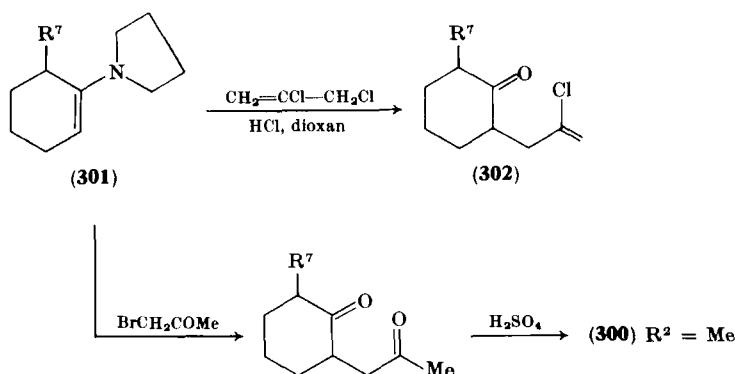
leads to ketone **289** ($R^1 = H$, $R^2 = Me$) (90% yield).⁷⁰⁴ With $R = Ph$, the same reaction leads to 2-phenyl-5-oxo-5,6,7,8-tetrahydro4*H*-chromene (**299**).⁷⁰⁴

Michael addition of nitroolefins to 1,3-cyclohexanediones gives, e.g., compound **289** ($R^2 = Me$, $R^6 = Me^2$, $R^3 = Ph$).⁷⁰⁵

b. *Synthesis of 4,5,6,7-Tetrahydrobenzofuran Derivatives.* The common point of the methods in this group is that they lead, by various routes, to a 1,4-diketone (2-acetyl-cyclohexanone), which undergoes ring closure in H_2SO_4 to the corresponding 4,5,6,7-tetrahydrobenzofuran derivative (**300**).



i. *Methods with enamines.* Condensation of 1-(1-cyclohexenyl)pyrrolidine (**301**, $R^7 = H$ or Me) with 2,3-dichloropropene, in the presence of HCl in dioxan, gives 2-(2-chloroallyl)cyclohexanone (**302**) (48% yield). Treatment with H_2SO_4 forms the 4,5,6,7-tetrahydrobenzofuran derivative (**300**, $R^2 = Me$, $R^7 = H$ or Me)⁷⁰⁶ (the intermediate γ -diketone is not isolated).



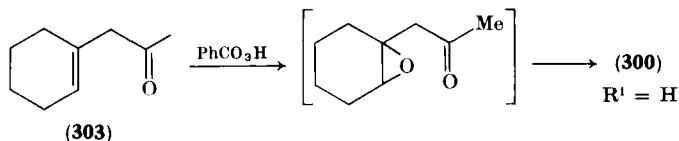
⁷⁰⁴ K. E. Schulte, J. Reisch, and A. Mock, *Arch. Pharm. (Weinheim)* **295**, 645 (1962); *Chem. Abstr.* **59**, 1575 (1963).

⁷⁰⁵ A. T. Nielsen and T. G. Archibald, *Tetrahedron* **25**, 2393 (1969).

⁷⁰⁶ J. Nienhouse, R. M. Irwin, and G. R. Ficini, *J. Amer. Chem. Soc.* **89**, 4557 (1967).

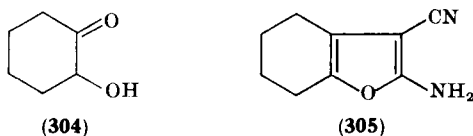
Similarly, condensing enamine (**301**, $R^7 = H$) with bromoacetone affords a 1,4-diketone, which with H_2SO_4 gives 2-methyl-4,5,6,7-tetrahydrobenzofuran (**300**, $R^1 = H$, $R^2 = Me$).⁷⁰⁷

ii. *Methods through epoxy intermediates.* Oxidation of cyclohexenylacetone (**303**) with perbenzoic acid, followed by ring closure in acidic



medium (catalyst), leads to the tetrahydrobenzofuran (**300**).⁷⁰⁸ A derived method can be applied to cycloheptanones.⁷⁰⁹

iii. *Reaction of α -hydroxy ketones with malononitrile.* This is a general method for preparing α -amino- β -cyanofurans. Its application to α -hydroxylated cyclanones, such as adipoin (**304**) (in the presence of triethylamine in methanol) leads to 2-amino-3-cyano-4,5,6,7-tetrahydrobenzofuran (**305**) (51% yield).⁷¹⁰



iv. *Application of the Nef reaction.* Condensation of a nitroolefin (**306**, $n = 4, 5$, or 6) with a β -ketonic ester (**307**) and subsequent treatment with acid leads (with $n = 4$) to the furan derivative **309** via diketone **308**. With nitroolefin (**306**, $n = 4$), the method gives 3-carbethoxy-2-methyl(or 2-ethyl)-4,5,6,7-tetrahydrobenzofurans (**309**).^{711,712} Hydrolysis and decarboxylation of the acids (Cu chromite + quinoline) affords compounds **300** ($R^2 = Me$ or Et , $R^1 = H$).⁷¹² The same compound (**309**, $R^2 = Me$) can be obtained by reaction of ethyl acetoacetate (1 hour at 60°) with 2-acetoxy-3-bromocyclohexene.⁷¹³⁻⁷¹⁵

⁷⁰⁷ H. F. Baumgarten, P. L. Creger, and C. E. Villars, *J. Amer. Chem. Soc.* **80**, 6609 (1958).

⁷⁰⁸ H. Fritel and P. Baranger, *C. R. Acad. Sci.* **241**, 674 (1955).

⁷⁰⁹ C. Iwanoff, *Chem. Ber.* **87**, 1600 (1954).

⁷¹⁰ K. Gewald, *Chem. Ber.* **99**, 1002 (1966).

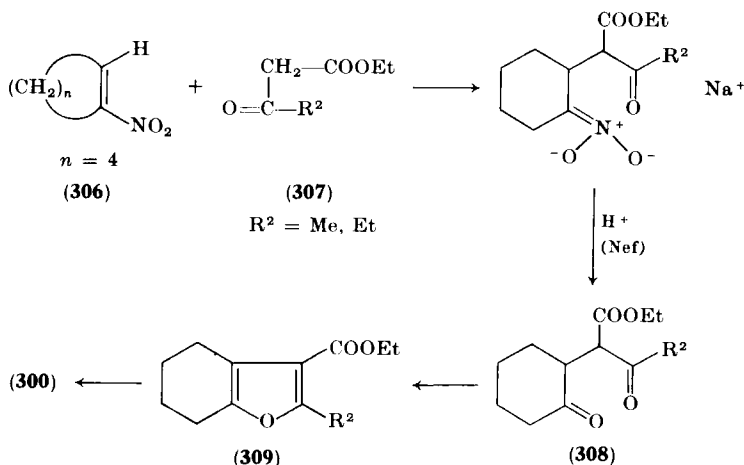
⁷¹¹ G. R. Schultze and F. Boberg, German Patent 965,408 (1957) *Chem. Abstr.* **53**, 16150 (1959).

⁷¹² F. Boberg and A. Kieso, *Justus Liebigs Ann. Chem.* **626**, 71 (1959).

⁷¹³ I. V. Machinskaya and V. A. Barkhash, *Zh. Obshch. Khim.* **27**, 1978 (1957); *Chem. Abstr.* **52**, 4615 (1958).

⁷¹⁴ I. V. Machinskaya and V. A. Barkhash, *Khim. Prom.* **2**, 135 (1957); *Chem. Abstr.* **52**, 6305 (1958).

⁷¹⁵ I. V. Machinskaya and V. A. Barkhash, *J. Gen. Chem. USSR* **27**, 2038 (1957).

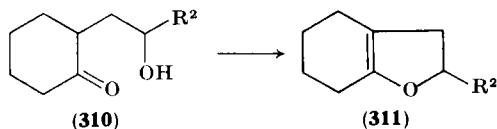


v. 1,4 Addition of carbethoxycarbene to α -ethoxymethylene ketones. Storm's method³⁴³ (Section IV, A, 3, b, iii), applied to α -ethoxymethylencyclohexanone, leads to compound **300** ($\text{R}^2 = \text{COOEt}$, $\text{R}^1 = \text{H}$), which is reduced by LiAlH_4 to **300** ($\text{R}^2 = \text{CH}_2\text{OH}$, $\text{R}^1 = \text{H}$).⁷¹⁶

3. 2,3,4,5,6,7-Hexahydrobenzofurans

Most syntheses of 2,3,4,5,6,7-hexahydrobenzofurans (**311**) are mere variations of the above-mentioned methods.

a. *Ring Closure of γ -Hydroxylated Cyclanones.* Compounds **311** are formed by ring closure (azeotropic distillation) of 2-(2-hydroxyethyl)-cyclohexanones (**310**),⁷¹⁷⁻⁷¹⁹ in the same way as compounds **300** are formed by ring closure of 1,4-diketones.



A variation of this synthesis involving enamines is the condensation of cyclohexenyl-pyrrolidine (**301**) with styrene oxide (reflux DMF) to give compound **311** ($\text{R}^2 = \text{Ph}$) by distillation of the intermediate perhydro derivative **312** from oxalic acid.⁷²⁰

⁷¹⁶ Sumitomo Chem. Co. Ltd., German Offen. 2,016,608 (1969); *Chem. Abstr.* **74**, 53503 (1971); Japanese Patent 7,206,614 (1972); *Chem. Abstr.* **77**, 19519 (1972).

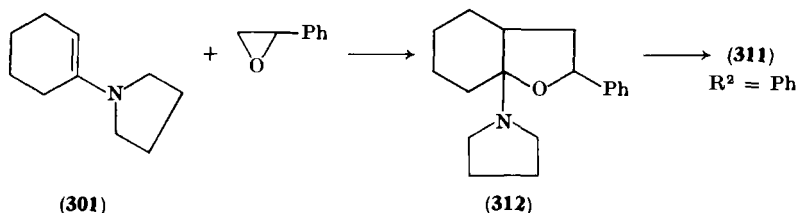
⁷¹⁷ V. G. Grosso, Ph. D. Thesis, St John's University, 1971.

⁷¹⁸ W. E. Harvez and D. S. Tarbell, *J. Org. Chem.* **32**, 1679 (1967).

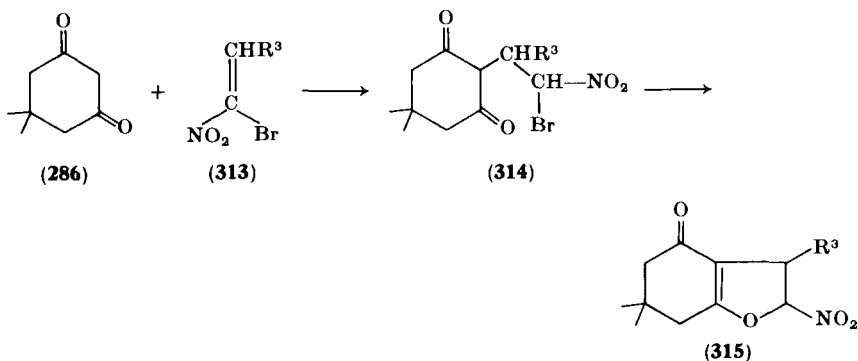
⁷¹⁹ L. H. Brannigan and D. S. Tarbell, *J. Org. Chem.* **35**, 639 (1970).

⁷²⁰ P. Jacobsen and S. Lawesson, *Tetrahedron* **24**, 3671 (1968).

In an application of the Nikl reaction,⁴⁷⁴ the alkylation of 1,3-cyclohexanedione with *trans*-1,4-dibromo-2-methyl-2-butene (a reaction previously mentioned in connection with compound **218** (Section IV,A,3,c,iv) leads to a similar product, without methyl groups in position 6.⁷²¹



b. *Condensation of 1,3-Cyclohexanediones (286) with Nitroolefins.* This reaction can give different products according to the conditions and the structures of the reagents. The condensation of ketones **286** with bromonitroolefins, depending on the conditions, leads to 2-nitro-2,3,4,5,6,7-hexahydro-benzofuran-4-ones (**315**) or to ketones **289**. Thus dimedone condensed with 1-bromo-1-nitroethylene (**313**, $R^3 = \text{H}$), gives the diketone **314**, which undergoes ring closure (Et_3N in benzene) to ketone **315** ($R^3 = \text{H}$) (90% yield).⁷²² Compounds with $R^3 = \text{Me}$,⁷²³ $R^3 = n\text{-Pr}$,⁷²⁴ $R^3 = \text{Ph}$,^{724,725} $R^3 = m\text{-NO}_2\text{C}_6\text{H}_4$ ⁷²⁴ or $p\text{-NO}_2\text{C}_6\text{H}_4$ ⁷²⁵



⁷²¹ F. Korte, D. Scharf, and K. H. Büchel, *Justus Liebigs Ann. Chem.* **664**, 97 (1963).

⁷²² V. M. Berestovitskaya, A. S. Sopova, and V. V. Perekalin, *Khim Geterotsikl. Soedin.*, 396 (1967); *Chem. Abstr.* **68**, 29501 (1968).

⁷²³ A. S. Sopova, V. V. Perekalin, and V. M. Lebednova, *Zh. Obshch. Khim.* **33**, 2143 (1963); *Chem. Abstr.* **59**, 13915 (1963).

⁷²⁴ A. S. Sopova, V. V. Perekalin, and Y. S. Bobovich, *Zh. Obshch. Khim.* **31**, 1528 (1963); *Chem. Abstr.* **55**, 22280 (1961).

⁷²⁵ A. S. Sopova, V. V. Perekalin, and V. M. Lebednova, *Zh. Obshch. Khim.* **34**, 2638 (1964).

TABLE XVIII
 2,3,4,5,6,7-HEXAHYDROBENZOFURANS

Benzofuran	References
<i>From 2-(2-hydroxyethyl)cyclohexanones</i>	
No Substituent	718
2-Me	718
2-Ph	720
2,2-DiMe	719
<i>From 1,3-cyclohexanediones and bromonitroalkenes</i>	
2-NO ₂ 4-O 6,6-diMe	722
2-NO ₂ 4-O 3,6,6-triMe	723
2-NO ₂ 4-O 3-Ph	723, 724
2-NO ₂ 4-O 3- <i>n</i> -Ph	724
2-NO ₂ 4-O 3- <i>m</i> (and <i>p</i>)NO ₂ C ₆ H ₄	724, 725
<i>From 1,3-cyclohexanediones and nitroalkenes</i>	
3-Ph 2-hydroxyimino	705, 727
3- <i>p</i> -BrC ₆ H ₄ 2-hydroxyimino	728

have been obtained in the same way. In the presence of a large excess of Et₃N, ketones **289** are obtained by denitration.^{722,723,726}

Condensation of ketones (**286**) with β -nitroolefins, R³CH=CR²NO₂ varies according to the nature of R² (H or Me). With compounds of type R³CH=CHNO₂ (R³ = Me,⁷⁰⁵ Ph,^{705,727} *p*-BrC₆H₄⁷²⁸) the structure of the product of the "abnormal Michael condensation" (in the presence of NaOMe + MeOH) of 1,3-cyclohexanediones and β -nitrostyrene gave rise to controversy: structures **316**,^{722,729} **317**,⁷⁰⁵ **318**,⁷³⁰ were advanced, but structure **319** has recently been established by X-ray crystallography.⁷²⁷ The intermediate compound **320** has also been isolated.⁷⁰⁵

The condensation (already mentioned in Section IV,B,2,a of 2-nitro-1-phenylpropene with dimedone leads to 6,7-dihydro-3-phenyl-2,6,6-trimethyl-4(5*H*)-benzofuranone (**321**).⁷⁰⁵

c. *Ichikawa Reaction*.^{731,732} The oxymercureal derivative of propylene

⁷²⁶ O. I. Yurchenko, A. S. Sopova, V. V. Perekalin, V. M. Beresto-Vitskaja, A. S. Polyanskaya, and N. T. Abolskalova, *Dokl. Akad. Nauk. SSSR* **171**, 1123 (1966).

⁷²⁷ S. J. Dominianni, M. O. Chaney, and N. D. Jones, *Tetrahedron Lett.*, 4375 (1970).

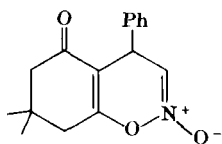
⁷²⁸ G. B. Ansell, D. W. Moore, and A. T. Nielsen, *J. Chem. Soc. B*, 2376 (1971).

⁷²⁹ H. Stetter and K. Hoehne, *Chem. Ber.* **91**, 1344 (1958).

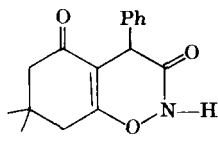
⁷³⁰ H. O. Larson, E. C. Ooi, A. K. Q. Siu, K. H. Hollenbeak, and F. L. Cue, *Tetrahedron* **25**, 4005 (1969).

⁷³¹ K. Ichikawa, O. Ittah, and J. Kawamura, *Bull. Chem. Soc. Jap.* **41**, 1204 (1968).

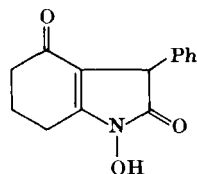
⁷³² S. Uemura, J. Nakano, and K. Ichikawa, *Nippon Kagaku Zasshi* **89**, 203 (1968); *Chem. Abstr.* **69**, 51913 (1968).



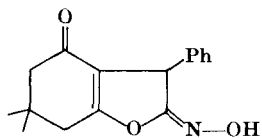
(316)



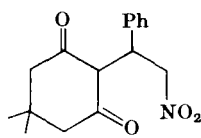
(317)



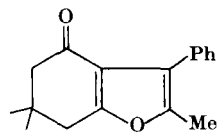
(318)



(319)



(320)

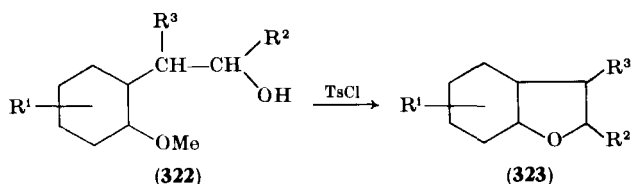


(321)

reacts with dimedone, giving 2,6,6- and 3,6,6-trimethyl-2,3,4,5,6,7-hexahydrobenzofuran-4-ones with demercuration.

4. Perhydrobenzofurans

a. *Ring Closure of 1,4-Dihydroxy or 1,4-Hydroxymethoxy derivatives.* Generally, compounds **323** are obtained from 2-(2-methoxycyclohexyl)ethanols (**322**) by the action of toluene-*p*-sulfonyl chloride in pyridine.



Compounds **322** (cis and trans) lead, respectively, to the cis and trans perhydrobenzofurans (**323**).^{733,734} Compound **323** ($R^3 = R^4 = \text{Me}$, $R^2 = \text{CH}_2\text{-CH}_2\text{-CHMe}_2$, $R^7 = \text{OTs}$) has also been obtained in this way.²¹⁴

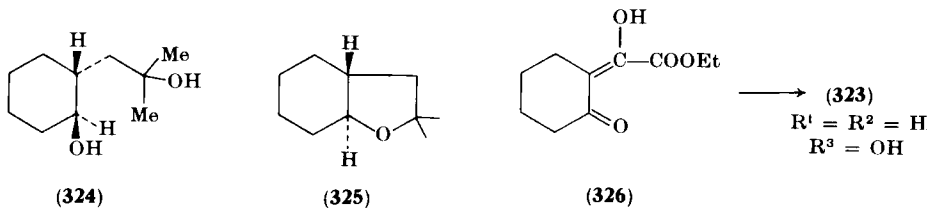
The *trans*-1,4-diol (**324**), heated in DMSO (20 hours at $165^\circ\text{--}180^\circ$), gives *trans*-2,2-dimethylperhydrobenzofuran (**325**) (78% yield).⁷³⁵ 3-Hydroxyperhydrobenzofuran (**323**, $R^2 = R^1 = \text{H}$, $R^3 = \text{OH}$) is obtained by treatment of 2-ethoxalylcyclohexanone (**326**) with LiAlH_4 .⁷³⁶

⁷³³ S. E. Cantor and D. S. Tarbell, *J. Amer. Chem. Soc.* **86**, 2902 (1964).

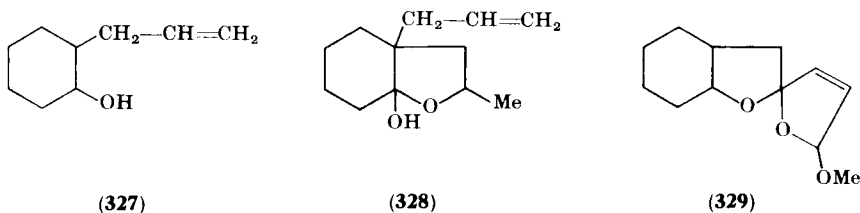
⁷³⁴ M. J. Garguilo, Y. Yamamoto, and D. S. Tarbell, *J. Org. Chem.* **36**, 846 (1971).

⁷³⁵ A. I. Meyers and K. Baburao, *J. Heterocycl. Chem.* **1**, 203 (1964).

⁷³⁶ H. Jäger and W. Färber, *Chem. Ber.* **92**, 2492 (1959).



2-Allylcyclohexanol (**327**) undergoes ring closure (85% H_3PO_4) to *cis*- and *trans*-2-methyloctahydrobenzofuran (**323**, $R^1 = R^3 = H$, $R^2 = Me$).⁷³⁷ Similarly 2,2-diallylcyclohexanone gives (H_2SO_4 at -10°) compound **328**.⁷³⁸



Electrolysis of 2-furfurylcyclohexanol in methanol gives the spiro compound **329**.⁷³⁹

C. FUSION OF THE BENZENE RING TO A FURAN SUBSTRATE

The methods in this group, far less numerous than the previous ones, involve the formation of the benzene ring by ring closure of furan derivatives with saturated or unsaturated side chains.

1. Intramolecular Ring Closure of ω -Furylalkanoic Acids (or Acid Chlorides)

Ring closure of substituted 3-(2-furyl)butyric acids and 3-(3-furyl)butyric acids (or their chlorides) should lead to 4,5,6,7-tetrahydrobenzofuran-4(or 7)-ones. The former should give the corresponding 4-hydroxybenzofurans or benzofurans (by reduction and dehydrogenation). While the ring closure of 3-(5-methyl-2-furyl)butyryl chloride (**330**, $R = Me$) actually affords **331** ($R = Me$; 77% yield),⁷⁴⁰ the

⁷³⁷ J. Colonge and F. Collomb, *Bull. Soc. Chim. Fr.*, 241 (1951).

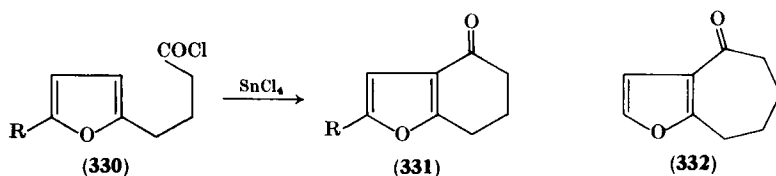
⁷³⁸ B. Bobranski, J. Pomarski, W. Roman, and Z. Zwirrello, *Rocz. Chem.* **43**, 1725 (1969); *Chem. Abstr.* **71**, 70163 (1969).

⁷³⁹ A. A. Ponomarev and I. A. Markushina, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 195 (1965); *Chem. Abstr.* **63**, 8293 (1965).

⁷⁴⁰ D. A. H. Taylor, *J. Chem. Soc.* 2767 (1959).

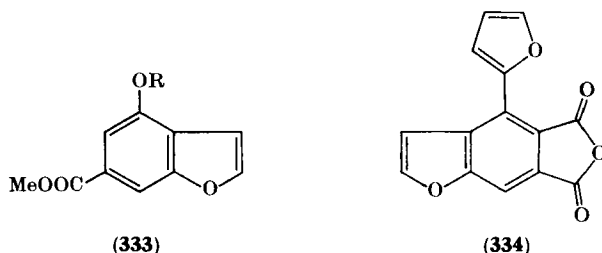
reaction has not been extended to, e.g., 3-(2-furyl)butyric acid or 3-(3-furyl)butyric acid.

4-(2-Furyl)valeryl chloride gave the expected ketone (**332**) in 60% yield.⁷⁴¹



2. Ring Closure of Furan Derivatives with Unsaturated Side Chains

a. *Ring Closure of Alkylidene-Succinic Acids.* Stobbe condensation of furfural with succinic esters⁷⁴² gives alkylidene-succinic acids, the ring closure of which gives benzofuran derivatives. Thus, *cis*-3-carbometh-



oxy-4-(2-furyl)-3-butenic acid undergoes quantitative ring closure (Ac_2O , NaOAc) to methyl 4-acetoxybenzofuran-6-carboxylic acid (**333**, $\text{R} = \text{Ac}$);⁷⁴³ the latter is converted into 4-methoxybenzofuran-6-carboxylic acid, which is readily decarboxylated to 4-methoxybenzofuran. Pyrolysis of difurfurylidene-succinic acid leads to 4-(2-furyl)benzofuran-5,6-dicarboxylic anhydride (**334**).⁷⁴³ Stobbe condensation of furfural with diethyl succinate (Ac_2O , NaOAc , AcOH) can lead directly to 4-hydroxybenzofuran-6-carboxylic acid (**333**, $\text{R} = \text{H}$),⁵⁶³ and with sodium succinate, to 4-hydroxybenzofuran (karanjol) (20% yield).⁷⁴⁴

b. *Photochemical Ring Closure of (2-Furyl)ethylene Derivatives.* The compounds prepared are of type **335–337**. Photochemical ring closure of

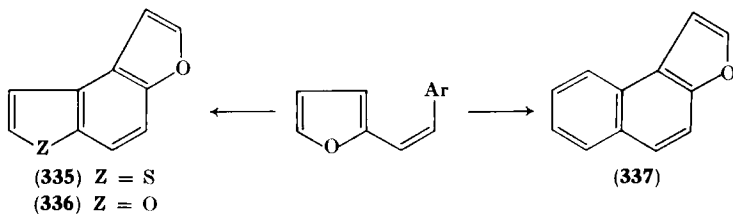
⁷⁴¹ W. Treibs and W. Heyer, *Chem. Ber.* **87**, 1197 (1954).

⁷⁴² W. S. Johnson and G. H. Daub, *Org. React.* **6**, 50 (1951).

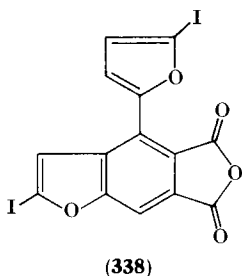
⁷⁴³ S. M. Abdel-Whahab and L. S. El Assal, *J. Chem. Soc. C*, 867 (1968).

⁷⁴⁴ C. P. J. Spruit, *Rec. Trav. Chim.* **81**, 813 (1962).

1-(2-furyl)-2(2-thienyl)ethylene in the presence of an oxidant gives thieno[3,2-*e*]benzofuran (**335**).^{745,746} Similarly, *trans*-1,2-di(2-furyl)ethylene (Ar = 2-furyl) gives furo[3,2-*e*]benzofuran (**336**), while *cis*-2-styrylfuran (Ar = Ph) gives naphtho[2,1-*b*]furan (**337**) (9% yield).⁷⁴⁶



c. *Ring Closure of (2-Furyl)acetylene Derivatives.* (5-Iodo-2-furyl)-propionic acid, heated with Ac₂O, gives 2-iodo-4-(5-iodo-2-furyl)benzofuran-5,6-dicarboxylic anhydride (**338**) (74% yield).⁷⁴⁷



d. *Ring Closure by Diene Synthesis.* The diene synthesis makes it possible to convert furan derivatives with unsaturated side chains into benzofuran derivatives. Thus, 2-propenylfuran, condensed with maleic anhydride, leads to three compounds, among which is 6-methyl-3a,4,5,6-tetrahydrobenzofuran-4,5-dicarboxylic acid anhydride (**339**).⁷⁴⁸ 2-Vinylfuran and dimethyl acetylenedicarboxylate give a 1:1 mixture of diesters **340** and **341** (10% total yield),⁷⁴⁹ together with a third compound (**342**) if the reaction is performed at a higher temperature. Compound **341** is formed *in situ* from the expected adduct.

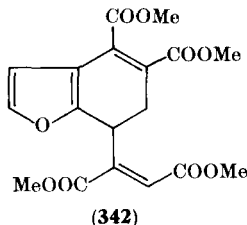
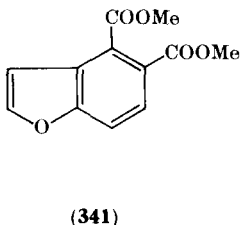
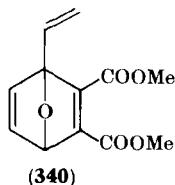
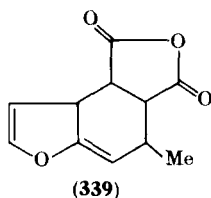
⁷⁴⁵ R. M. Kellogg, M. B. Groen, and H. Wynberg, *J. Org. Chem.*, **32**, 3093 (1967).

⁷⁴⁶ C. E. Loader and C. J. Timmons, *J. Chem. Soc. C*, 1677 (1967).

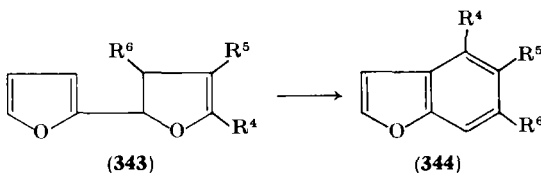
⁷⁴⁷ L. I. Vereshchagin, S. P. Korshinov, B. L. Bel'Shed Vorskaya, and T. V. Lipovich, *Zh. Org. Khim.*, **2**, 522 (1966); *Chem. Abstr.*, **65**, 7124 (1966).

⁷⁴⁸ C. Schmidt, *Naturwissenschaften*, **40**, 581 (1953).

⁷⁴⁹ W. J. Davidson and J. A. Elix, *Tetrahedron Lett.*, 4589 (1968).



e. *Thermal Ring Closure.* 2,3-Dihydro-2,2'-difuryl derivatives (343) give benzofurans (344) at 200°C. in the presence of Pd/Al₂O₃.⁷⁵⁰ Benzofuran and its 4- and 6-methyl derivatives have thus been prepared in 70% yields, while 5-methylbenzofuran was obtained (35% yield) as a mixture with an isomeric ethylenic aldehyde.⁷⁵¹



3. Extension to Fused Diheterocyclic Compounds

While the synthesis of benzofuran derivatives from suitable furan derivatives has been comparatively little investigated, the synthesis of fused two-ring and three-ring compounds containing a pyridine nucleus from furan derivatives has been more successful: furo[3,2-*c*]pyridines (345),^{752,753} 2,3-dihydrofuro[2,3-*d*]quinolines (from 4,5-dihydro-3-furoic acid),⁷⁵⁴ acrophyllin (346), and 7-hydroxydictamnine (347) (from ethyl 2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate),⁷⁵⁵ are examples of compounds in this class which have been prepared.

⁷⁵⁰ G. Dana, P. Scribe, and J. P. Girault, *Tetrahedron Lett.*, 4137 (1970).

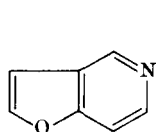
⁷⁵¹ J. P. Girault, P. Scribe, and G. Dana, *Bull. Soc. Chim. Fr.*, 2279 (1971).

⁷⁵² F. Eloy and A. Deryckere, *J. Heterocycl. Chem.* **8**, 57 (1971).

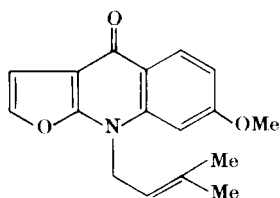
⁷⁵³ J. D. Bourzat and E. Bisagni, *Bull. Soc. Chim. Fr.*, 1727 (1971).

⁷⁵⁴ K. Yoshikata, *Yakugaku Zasshi* **81**, 1278 (1961); *Chem. Abstr.* **57**, 13743 (1962).

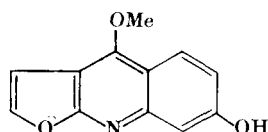
⁷⁵⁵ S. Prabhakar, B. R. Pai, and V. N. Ramachandran, *Indian J. Chem.* **8**, 857 (1970).



(345)



(346)



(347)

D. FORMATION OF THE BENZOFURAN NUCLEUS FROM OTHER HETEROCYCLIC COMPOUNDS

Three groups of methods are distinguished. In the first group, the starting molecule already has the desired skeleton, the initial compound being partially reduced benzofuran: 3(2*H*)-benzofuranone, 6,7-dihydro-4(5*H*)-benzofuranone, 2,3-dihydrobenzofuran, tetrahydrobenzofuran, hexahydrobenzofuran, or perhydrobenzofuran.

In the second group the starting molecule belongs to another class of oxygenated heterocycle, such as a coumarin, flavone, chroman, α,β -unsaturated γ -lactone, or δ -sultone.

A number of benzofuran derivatives are also formed by degradation of complex natural substances. These miscellaneous examples form the third group.

1. Benzofuran Derivatives from Hydrobenzofurans

a. *Benzofuran Derivatives from 3(2H)-Benzofuranones (237)*. Ketones (237) can lead to benzofurans either directly, or through the 2,3-dihydrobenzofurans.

Stoermer's method (1906) involves reduction of the oximes (Hg-Na in AcOH + EtOH) of 3(2*H*)-benzofuranones to give the corresponding benzofurans^{529,756} (Table XIX).

Reduction by metal hydrides (LiAlH₄, NaBH₄) of these benzofuranones gives 3-hydroxy-2,3-dihydrobenzofurans which are dehydrated by distillation or by treatment with an acid or with P₂O₅ or treating the 3-acetoxy derivative with trifluoroacetic acid.³⁹ The intermediates are more or less stable depending on their structures or their degree of purity: 3-hydroxy-2,3-dihydrobenzofuran, described by Stoermer as

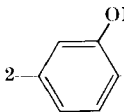
⁷⁵⁶ O. Dann, German Patents 959, 980 (1956); *Chem. Abstr.* **53**, 2257, 2258 (1959).

⁷⁵⁷ Y. Kawase and S. Nakamoto, *Pharm. Bull. Soc. Jap.* **4**, 170 (1961).

TABLE XIX
BENZOFURANS FROM 3(2*H*)-BENZOFURANONES

Benzofuran	References
<i>Reduction of oximes</i>	
6-OH	529
5-Et 6-OH	529
4,7-DiOMe 6-OH	756
<i>Reduction with NaBH₄</i>	
4-Me	276
5-Me	276
6-Me	276
7-Me	758
2-Me 5-NO ₂	39
2-Me 7-NO ₂	39
6-OMe	453
6,7-DiOMe	559
2-IsoPr 6-OMe	757
5-OMe 6,7-methylenedioxy	559
4,6,7-TriOMe	535
4,5,7-TriF 6-OMe	684
4,5,6,7-TetraF	680, 759
4,5,6,7-TetraOMe	559
2-Me 3-OH 2,3-dihydro (<i>cis</i> and <i>trans</i>)	39
2-IsoPr 3-OH 6-OMe 2,3-dihydro	757
<i>Reduction with Raney Ni</i>	
5-OMe 2,3-dihydro	516
5-OMe	516
<i>Reduction of acetoxy derivatives</i>	
4,6-DiOH 5-Ac 7-COOEt	538
6,7-DiOH	406, 760, 761
4,6-DiOH	761
6,7-DiOAc 2,3-dihydro	534
6-OAc 2,3-dihydro	515
<i>Reaction of Grignard reagents on 237</i>	
3-Me	276
3-Ph	239
<i>Reaction of Grignard reagents on 2(3<i>H</i>)-benzofuranones</i>	
2-Ph	394
2,3-diPh 4-Me	762, 763
2,3-diPh 4,5-diMe	762, 763
2,3-diPh 4,6-diMe	762, 763
2,3-diPh 4,7-diMe	762, 763
2,3-diPh 4-Me 6-isoPr	762, 763
2,3-diPh 4-Me 7-isoPr	762, 763

TABLE XX
BENZOFURANS FROM 2,3-DIHYDROBENZOFURANS

Benzofuran	References
<i>With NBS</i>	
4-Me 5-Ac 6-OAc	765, 766
4,6-DiOMe	765, 766
4-OMe 5-Ac 6-OH	765, 766
<i>With S at 220°C</i>	
2-Me 5,7-diOMe	10
2-Me 4,6-diOMe	10
2-Me 5-OMe	10
4,5,6,7-TetraCl	460
	4
<i>By catalytic dehydrogenation</i>	
No substituent	768
2-Me	769
2-Alkyl	770
6,7-DiOMe	761

the presence of benzoyl peroxide, which converts 2,3-dihydrofuran derivatives into bromo derivatives.^{530,765-767} The latter, treated with dimethylaniline or collidine, give the corresponding benzofurans (Table XX). The method has been widely used for polycyclic compounds: phenanthro[9,10-*b*]furan,^{771,772} furo[3,2-*b*]xanthone,^{610,773,774} furoflavone,⁴³⁴ furoquinolines.^{775,776} It is not general, however, and

⁷⁶⁴ T. R. Govindachari and S. Prabhakar, *Indian J. Chem.* **1**, 17 (1963).

⁷⁶⁵ T. A. Geissman, U.S. Patent 2,659,734 (1953); *Chem. Abstr.* **48**, 13722 (1954).

⁷⁶⁶ T. A. Geissman, T. G. Halsall, and E. Hinreiner, *J. Amer. Chem. Soc.* **72**, 4326 (1950).

⁷⁶⁷ A. J. Birch, M. Maung, and A. Pelter, *Aust. J. Chem.* **22**, 1923 (1969).

⁷⁶⁸ T. Lesiak, *Rocz. Chem.* **38**, 1015 (1964); *Chem. Abstr.* **62**, 2751 (1965).

⁷⁶⁹ E. A. Viktorova, E. A. Karakhanov, and E. G. Saginova, USSR Patent 203,696 (1967); *Chem. Abstr.* **69**, 43780 (1968).

⁷⁷⁰ E. A. Karakhanov, L. G. Saginova, and E. A. Viktorova, *USSR Geterogennyyi Katal. Reakt. Poluch. Prevrashch. Geterotsikl. Soedin.*, 81 (1971); *Chem. Abstr.* **76**, 99451 (1972).

⁷⁷¹ W. W. Sullivan, D. Ullman, and H. Shechter, *Tetrahedron Lett.*, 457 (1969).

⁷⁷² T. Anderson and W. M. Horspool, *J. Chem. Soc., Perkin Trans. I*, 536 (1972).

⁷⁷³ C. S. Angadiyavar and S. Rajagopal, *Monatsh. Chem.* **99**, 1014 (1968).

⁷⁷⁴ A. Jefferson and F. Scheinman, *J. Chem. Soc. C*, 175 (1966).

⁷⁷⁵ M. F. Grundon and N. J. McCorkindale, *J. Chem. Soc.*, 2177 (1957).

⁷⁷⁶ Y. Kuwayama, J. Ota, T. Mikasta, and H. Kanda, *Yakugaku Zasshi* **88**, 1050 (1968); *Chem. Abstr.* **70**, 29125 (1969).

failures have been reported in the furocoumarin^{50,535,777} and furoquinoline⁷⁷⁸ series.

Klarman's method⁷⁷⁹ of dehydrogenation of 2,3-dihydrobenzofurans is achieved with sulfur at 220° (45–85% yields)^{4,10} or with selenium.²¹⁴ The method has led to methoxybenzofurans which are difficult to obtain otherwise.¹⁰ It has been applied to polycyclic compounds: furoquinolines,^{223,780} naphtho[2,1-*b*]furan.⁴⁹⁹

Catalytic dehydrogenation over (Al₂O₃, Fe₂O₃) at 600°–630° in the presence of moist air converts 2,3-dihydrobenzofurans (78% yield) into benzofurans, with formation of phenolic compounds as by-products.^{768,769} Excellent yields are also obtained with Pd/C (reflux diphenyl oxide), Pt or Rh/C at 250°–350°,⁷⁷⁰ or Pd on norite.⁷⁶¹ The method can be applied to the preparation of naphtho[2,1-*b*]furans,⁴³⁶ furocoumarins^{515,539,777} (e.g., psoralene⁷⁸¹), furochromones,^{442,534} and 5*H*-benzofuro[4,5-*c*]benzopyran-5-one.⁴⁴¹

The reduction of ketones **237** by the Clemmensen and Wolff–Kishner–Huang–Minlon reactions has generally been unsatisfactory. However, 6-hydroxy-2,3-dihydrobenzofuran has thus been obtained in 55% yield from compound **237** (R⁶ = OH).⁵¹⁹

c. *Benzofurans from 6,7-Dihydro-4(5*H*)-benzofuranones (289) and from 4,5,6,7-Tetrahydrobenzofurans (300).* Like their isomers **237**, ketones **289** can lead to the benzofuran ring directly or through 4,5,6,7-tetrahydrobenzofurans, according to the method. Thus, on treatment with sulfur (25 minutes at 240°–245°), ketones **289** give the corresponding 4-hydroxybenzofurans.^{101,782} By the Semmler–Wolff reaction,^{223,782,783} the oximes of ketones **289** (Rⁱ = H) at 100° in Ac₂O + AcCl + pyridine give 4-acetamidobenzofurans.⁷⁸³ With excess pyridine hydrochloride, the oxime of **289** (R² = R³ = Me, Rⁱ = H) gives 4-amino-2,3-dimethylbenzofuran.^{223,784}

The methods for the synthesis of 4,5,6,7-tetrahydrobenzofurans (**300**)

⁷⁷⁷ E. C. Horning and D. B. Reisner, *J. Amer. Chem. Soc.* **72**, 1514 (1950).

⁷⁷⁸ M. F. Grondon and K. J. James, *Chem. Commun.*, 1427 (1970).

⁷⁷⁹ B. Klarman, *J. Amer. Chem. Soc.* **73**, 4476 (1951).

⁷⁸⁰ R. Royer, P. Demerseman, C. Pène, and G. Colin, *Bull. Soc. Chim. Fr.*, 920 (1966).

⁷⁸¹ D. K. Chatterjea and S. Salyanmay, *Sci. Cult.* **33**, 528 (1967); *Chem. Abstr.* **69**, 86859 (1968).

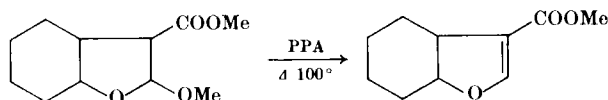
⁷⁸² P. Demerseman, J. P. Lechartier, C. Pène, A. Cheutin, R. Royer, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 1473 (1965).

⁷⁸³ A. N. Kost and L. G. Tret'yakova, USSR Patent 210,182 (1968); *Chem. Abstr.* **69**, 59088 (1968).

⁷⁸⁴ R. Royer, P. Demerseman, and C. Colin, *Bull. Soc. Chim. Fr.*, 1026 (1970).

have been mentioned previously (Section IV, B, 2, b). The same compounds can also be obtained by reduction of 6,7-dihydro-4(5*H*)-benzofuranones by the Wolff-Kishner method: the 2-phenyl,⁶⁹⁷ 2-methyl,⁶⁹² 3,6-dimethyl,^{699,700} 2,3-dimethyl,⁶⁹² and 2-methyl-3-carboxy derivatives have thus been obtained in 50–75% yields. Dehydrogenation of compounds **300** to the corresponding benzofurans is achieved with Pd/C at 240° or with sulfur at 190°–210°. With the 2-phenyl derivative (**300**, R¹ = H, R² = Ph), the yields are, respectively, 26%⁶⁹⁷ and 89%.⁶⁹⁶

d. *Benzofurans from 2,3,4,5,6,7-Hexahydrobenzofurans and from Perhydrobenzofurans.* Dehydrogenation is achieved with sulfur at 200° (benzofuran, 2-Me and 2-Ph derivatives)⁷³³ or with selenium.⁷³³ The perhydro derivatives may be previously converted into hexahydro derivatives as in the example of Scheme 6.

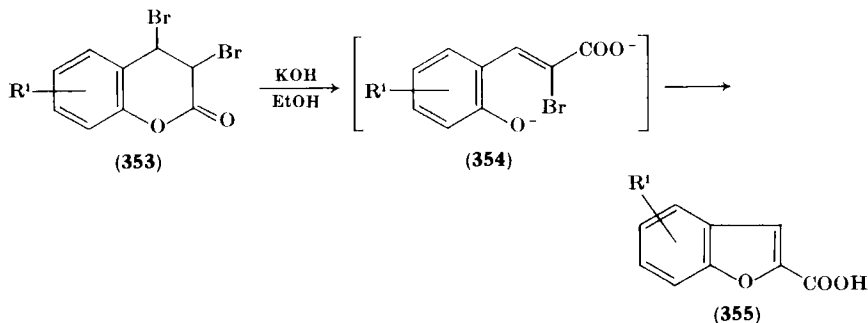


SCHEME 6

2. Benzofurans from Other Oxygen Heterocycles

a. *Synthesis of Benzofurans from Coumarins.* The Perkin-Wittig-Ebert ring-contraction reaction is of historical interest; Perkin thus effected the first synthesis of benzofuran in 1871 (from natural coumarin). Since then, numerous benzofurans have been prepared by it.

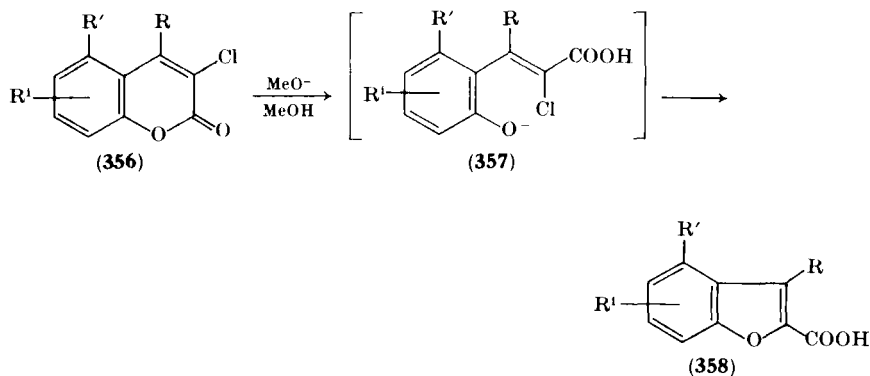
Alkaline degradation of coumarin dibromides (**353**) to coumarilic acids is effected in good yield by boiling aqueous ethanolic potassium or sodium hydroxide (82–88% with R¹ = H).⁷⁸⁵ This reaction makes it possible to obtain Bz-substituted coumarilic acids unsubstituted in



⁷⁸⁵ R. C. Fuson, J. W. Kneisley, and E. W. Kaiser, *Org. Syn.* **24**, 33 (1944).

position 3. Coumarilic acids (**355**) are readily decarboxylated to the corresponding benzofurans.

3-Halocoumarins also undergo the Perkin rearrangement under various conditions. Thus, heating 3-chlorocoumarins (**356**), substituted or unsubstituted, with sodium methoxide in methanol gives the corresponding methyl ester of carboxybenzofurans (**358**, $R^1 = H$).^{786,787}



The fact that 2-chloro-3-(2,6-dihydroxyphenyl)acrylic acid (**357**, $R' = OH$) was isolated from 3-chloro-5-hydroxycoumarin⁷⁸⁶ confirms the mechanism of the Perkin coumarilic rearrangement. Depending on the conditions, degradation can lead either to the coumarilic acid (boiling alcoholic KOH or NaOH)^{788,789} or directly to the benzofuran derivative (aqueous Na_2CO_3) along with the corresponding coumarilic acid.⁷⁹⁰

If the coumarin is heated with an amine, the amide of the coumarilic acid is isolated: thus, 3-halo-4-piperidinocoumarins with piperidine ($X = CH_2$) or morpholine ($X = O$) gives the corresponding compounds **359**.⁷⁹¹

3-Halocoumarins may be prepared by several methods: von Pechmann condensation of polyphenols with ethyl chloroacetoacetate,⁷⁹²

⁷⁸⁶ A. Roedig and S. Schödel, *Chem. Ber.* **91**, 330 (1958).

⁷⁸⁷ M. S. Newman and C. K. Dalton, *J. Org. Chem.* **30**, 4126 (1965).

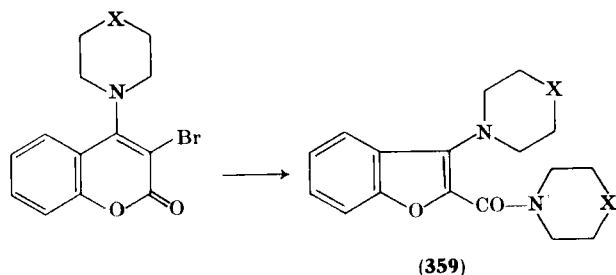
⁷⁸⁸ F. M. Dean, E. Evans, and H. Robertson, *J. Chem. Soc.*, 4565 (1954).

⁷⁸⁹ B. Libis and E. Habicht (Geigy AG), German Offen. 1,927,393 (1969); *Chem. Abstr.* **72**, 43425 (1970).

⁷⁹⁰ M. G. Marathey and K. G. Gore, *J. Univ. Poona Sci. Tech.* **16**, 37 (1959); *Chem. Abstr.* **54**, 9904 (1960).

⁷⁹¹ V. A. Zagorevskii, V. L. Salev'ev, L. M. Meshcheryakova, and V. G. Vinokurov, *Khim. Geterotsikl. Soedin. Sb.* **2**, **2**, 166 (1970); *Chem. Abstr.* **76**, 140378 (1972).

⁷⁹² N. M. Shah and P. M. Shah, *Chem. Ber.* **93**, 18 (1960).



reaction of SO_2Cl_2 on the corresponding coumarin,⁷⁹³ bromination of 4-methylcoumarins in acetic acid,⁷⁹⁰ on ring closure (H_2SO_4 at 0°) of β -aldehyde-esters of general formula $\text{Ar}-\text{O}-\text{CO}-\text{CHX}-\text{CHO}$ ($\text{X} = \text{Cl}$ or Br)^{794,795} (Table XXI).

4-Chlorocoumarins also give the Perkin rearrangement, but the results vary according to conditions. Thus, 4-chlorocoumarin gives 4-methoxycoumarin ($\text{MeOH} + \text{MeONa}$),⁸⁰⁴ will give with NaOH (in water + dioxan) *o*-hydroxypropionic acid at 20° (92.5% yield), but benzo-furan-2-carboxylic acid at the boiling point (80% yield).^{803,804} The method also affords 4,5,6,7-tetrahydrobenzofuran derivatives [3-chloro-5-oxo-5,6,7,8 tetrahydrocoumarin (360) gives 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylic acid (361)⁷⁹⁶] and fused benzofurans (naphtho[2,1-*b*]furan,^{794,795} 5-hydroxy-3-methylnaphtho[1,2-*b*]furan,⁸⁰⁷ 3,8-dimethyl-5-hydroxyphenanthro[4,3-*b*]furan).⁸⁰⁷

⁷⁹³ V. A. Zagorevskii, V. L. Savel'ev, and V. G. Vinokurov, *Khim. Geterotsikl. Soedin. Sb.* 2, 4, 160 (1970); *Chem. Abstr.* 76, 140425 (1972).

⁷⁹⁴ M. Le Corre and E. Levas, *C. R. Acad. Sci.* 257, 1622 (1963).

⁷⁹⁵ M. Le Corre, *Ann. Chim. (Paris)* 14, 193 (1968).

⁷⁹⁶ J. Zergeny and E. Habicht, South African Patent 6,804,836 (1969); *Chem. Abstr.* 71, 81144 (1969).

⁷⁹⁷ E. Habicht, B. Libis, and J. Zergenyi (Geigy Jr. AG), South African Patent 7,007,819 (1971); *Chem. Abstr.* 76, 126787 (1972).

⁷⁹⁸ D. A. Zykov, G. A. Markova, Z. D. Kirsanova, M. M. Shestaeva, N. V. Kaverina, and V. A. Zagorevskii, *Khim. Farm. Zh.* 5, 23 (1971); *Chem. Abstr.* 76, 99430 (1972).

⁷⁹⁹ M. G. Marathey and J. M. Athavale, *J. Univ. Poona Sci. Tech.* 4, 94 (1953); *Chem. Abstr.* 49, 11638 (1955).

⁸⁰⁰ D. B. Limaye and T. B. Panse, *Rasayan* 2, 32 (1950); *Chem. Abstr.* 45, 6620 (1951).

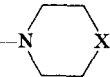
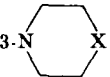
⁸⁰¹ Y. A. Shaika and K. N. Trivedi, *J. Indian Chem. Soc.* 48, 1041 (1971).

⁸⁰² V. A. Zagorevskii and Z. D. Kirsanova, *Khim. Geterotsikl. Soedin.* 4, 598 (1968); *Chem. Abstr.* 70, 35578 (1969).

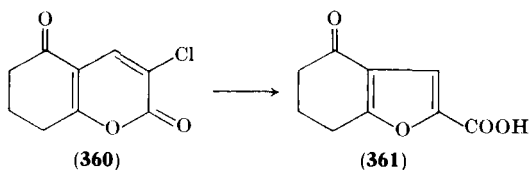
⁸⁰³ V. A. Zagorevskii and N. V. Dudykina, *Zh. Obshch. Khim.* 32, 2384 (1962).

⁸⁰⁴ V. A. Zagorevskii, V. L. Salev'ev and N. V. Dudykina, *Khim. Geterotsikl. Soedin. Sb.* 2, 155 (1970); *Chem. Abstr.* 76, 140433 (1972).

TABLE XXI
 SUBSTITUTED BENZOFURANS FROM COUMARINS

Starting compounds	Benzofurans	References
Coumarin dibromide (353)	2-COOH 6-Et	796
	2-COOH 6,7-diMe	797
3-Halocoumarins (356)	2-COOH 3-Me	793
	2-COOMe 3-Alk 5-Cl	787
	2-COOMe 4-OMe	786
	2-COOH 3-Me 5-Br 6-OH	792
	2-COOH 3-Me 4-OH 5-Ac 7-Et and 3-Me 4-OH 5-Ac 7-Et	790
	2-COOH 3-H(or Me) 5-H(or Br) 6-OMe 7-H(or Br)	798
	2-COOH 6,7-(O-CH ₂ -CH ₂ -O)	798
	2-COOH 5,6-(O-CH ₂ -CH ₂ -O)	798
	2-COOH 3,5-diMe 4,6-diOMe	788
	2-COOH 6-Cl 7-Me	789
	  (X = CH ₂ or O)	791
	3-Me 6-OH 7-CH ₂ Ph	799
	6-OH 7-COCH ₂ Ph	799
	3-Me 5-Cl 6-OH 7-COCH ₂ Ph	800
	6-OH 7-Ac	801
	3-Me 6-OH 7-COCH ₂ Ph	801
	4-OH 5-Ac 3,6-diMe	801
	5,6-DiOH	802
	2,3-DiCOOH 5,6-diOMe	805
	3-Ph,3-Ph-OMe,3-Ph 6,7-diOMe	806
4-Halocoumarins	2-COOH	803, 804

The Perkin reaction makes available Bz-alkyl Bz-hydroxyketones, which are difficult or impossible to obtain by other methods.⁷⁹⁹⁻⁸⁰¹ It also applies in the field of furocoumarins: 2-isopropylpsoralene (363), a

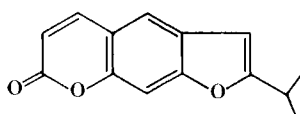


⁸⁰⁵ G. N. Holton, G. Parker, and A. Robertson, *J. Chem. Soc.*, 2049 (1949).

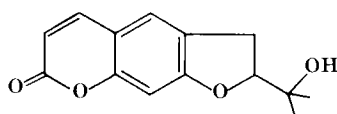
⁸⁰⁶ V. K. Ahluwalia, A. C. Mehta, and J. R. Seshadri, *Tetrahedron* **4**, 271 (1958).

⁸⁰⁷ T. J. King and G. Read, *J. Chem. Soc.*, 5090 (1961).

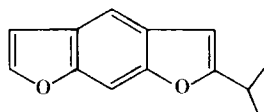
dehydration product of marmesine (362) (a natural substance), is brominated in the 3- and 6-positions and leads, through alkaline degradation, to the furocoumarilic derivative 364.⁸⁰⁸ 2,3-Dihydroxanthoxin (9-methoxy-2,3-dihydrofuro[3,2-f]benzofuran) and its 4-methoxy derivative⁸⁰⁹ are brominated in the 6-position and on alkali treatment and decarboxylation give 8-methoxy-2,3-dihydrofuro[3,2-f]benzofuran (365) (and its methoxy derivative), which establishes the structure of the brominated compound.^{35,535} More complex diheterocyclic polycyclic compounds have also been synthesized by this method.⁸¹⁰



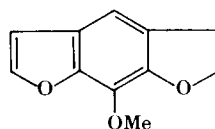
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(362)

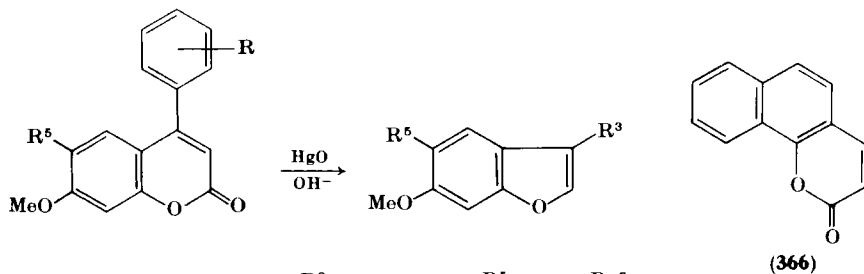


(364)



(365)

Oxidation of coumarins (HgO, alkaline medium) can lead directly to benzofuran derivatives. The method seems to be fairly general^{806,811} for 3-arylbenzofurans (see Scheme 7).



SCHEME 7

⁸⁰⁸ E. A. Abu Mustafa and M. B. E. Fayed, *Tetrahedron* **23**, 1305 (1967).

⁸⁰⁹ K. D. Kaufman and L. R. Worden, *J. Org. Chem.* **25**, 2222 (1960).

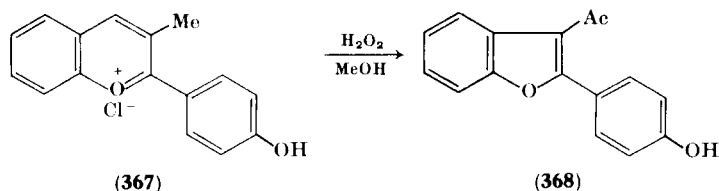
⁸¹⁰ T. Ohta and Y. Mori, *Pharm. Bull. Tokyo* **5**, 80 (1957); *Chem. Abstr.* **52**, 1158 (1958).

⁸¹¹ T. Saroja, J. R. Seshadri, and S. K. Mukerjee, *Indian J. Chem.* **9**, 1316 (1971).

Two failures of the Perkin reaction should be reported: 5-nitrocoumarin gives a 3,4-dibromide, but alkaline treatment does not lead to 5-nitrocoumarilic acid,⁸¹² further, 2*H*-naphtho[1,2-*b*]pyran-2-one (366) is brominated not on the heterocycle, but in position 6.⁸¹³

Transition from a chromenoid skeleton to a benzofuran has also been achieved by other means. We may mention the photooxidation of rotenone⁸¹⁴ and the preparation of 5,6-dimethoxybenzofuran by electronic impact on 6,7-dimethoxycoumarin.⁸¹⁵ The Koelsch reaction is kindred; it converts coumarine into 2,3-dihydrobenzofuran derivatives.⁸¹⁶

b. *Synthesis of Benzofurans from Flavylum Salts and from Flavonoid Derivatives.* Those methods are mainly used for preparing 2-arylbenzofurans.⁸¹⁷ 3-Alkyl-, 3-alkoxy-, and 3-aryloxyflavylum salts lead, by oxidation with peroxides, to 3-acyl 2-arylbenzofurans and 2-arylbenzofuran-3-carboxylic acids. Thus, 3-methyl-4'-hydroxyflavylum chloride (367), with H₂O₂ in MeOH, gives 3-acetyl-2-(4-hydroxyphenyl)benzofuran (368),⁸¹⁷ which is converted (haloform reaction followed by



decarboxylation) into 2-(4-hydroxyphenyl)benzofuran. Coumestrol (4) has been obtained by oxidation of 7,2',4'-trihydroxy-3-methoxyflavylum chloride.⁸¹⁸ 2-Phenylbenzofurans have been synthesized by this method.⁸¹⁸⁻⁸²⁰

c. *Synthesis of Benzofurans from Chroman Derivatives.* Some chroman derivatives undergo ring contraction on protracted boiling in acid.

⁸¹² D. Papa, E. Schwenk, and H. F. Ginsborg, *J. Org. Chem.* **16**, 253 (1951).

⁸¹³ P. Emmott and R. Livingstone, *J. Chem. Soc.*, 3144 (1957).

⁸¹⁴ M. Chubachi and M. Hamada, *Tetrahedron Lett.*, 3537 (1971).

⁸¹⁵ H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, p. 256. Holden-Day, San Francisco, 1964.

⁸¹⁶ C. F. Koelsch, *J. Amer. Chem. Soc.* **67**, 569 (1945).

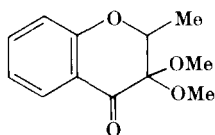
⁸¹⁷ L. Jurd, *Chem. Ind. (London)* **13**, 1165 (1963).

⁸¹⁸ L. Jurd, U.S. Patent 3,147,280 (1963); *Chem. Abstr.* **61**, 11974 (1964).

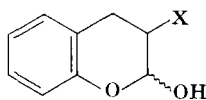
⁸¹⁹ L. Jurd, *J. Org. Chem.* **29**, 2602 (1964).

⁸²⁰ L. L. Simonova and A. A. Shamshurin, *Khim. Priir. Soedin.* **3**, 367 (1967); *Chem. Abstr.* **68**, 68908 (1968).

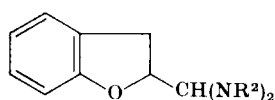
Thus, 2-methylbenzofuran-3-carboxylic acid has been obtained from compound **369**.⁵⁴³



(369)

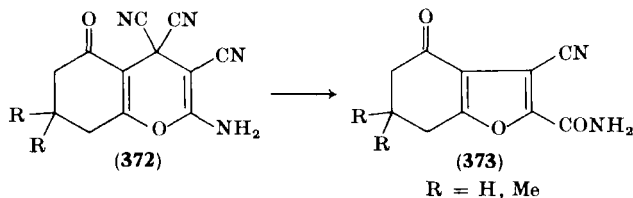


(370)



(371)

Halohydrins of type **370** (X = halogen) with piperidine or morpholine give compound **371**.⁸²¹ Compound **372** (obtained by tetracyanoalkylation of dihydroresorcinol) is ring contracted by 10% NaOH to com-



pound **373**.⁸²² Thermolysis of chroman itself (Al_2O_3 , 250–350°) gives 2-methyl benzofuran.⁸²³

d. *Synthesis of Benzofurans from Flavanones, Flavans, and Flavanols.* By reflux heating in excess of NaOH/EtOH, flavanones (**374**) lead to 2-aroil-3-hydroxybenzofurans (**375**) (X and Y = Cl or Br).^{824–828} 3,4-Dihydroxyflavans (leucoanthocyanidins) (**376**) are oxidized by lead tetraacetate^{829,830} to 2-formyl-3-hydroxy-2-phenyl-2,3-dihydrobenzofurans (**377**), which undergo spontaneous cleavage in acidic medium to benzofurans (**378**).

⁸²¹ G. Descotes and D. Missos, *Bull. Soc. Chim. Fr.*, 696 (1972).

⁸²² H. Junek and H. Aigner, *Z. Naturforsch. B* **25**, 1423 (1970); *Chem. Abstr.* **74**, 53469 (1971).

⁸²³ E. A. Karakhanov, N. N. Khvorostrikhina, and E. A. Viktorova, *Vestn. Mosk. Univ. Khim.* **11**, 635 (1970).

⁸²⁴ H. K. Pendse and N. D. Patwardhan, *Rasayanam* **2**, 117 (1956); *Chem. Abstr.* **51**, 5062 (1957).

⁸²⁵ S. D. Limaye, H. K. Pendse, K. R. Chanderkar, and G. V. Bhide, *Rasayanam* **2**, 97 (1956); *Chem. Abstr.* **51**, 2990 (1957).

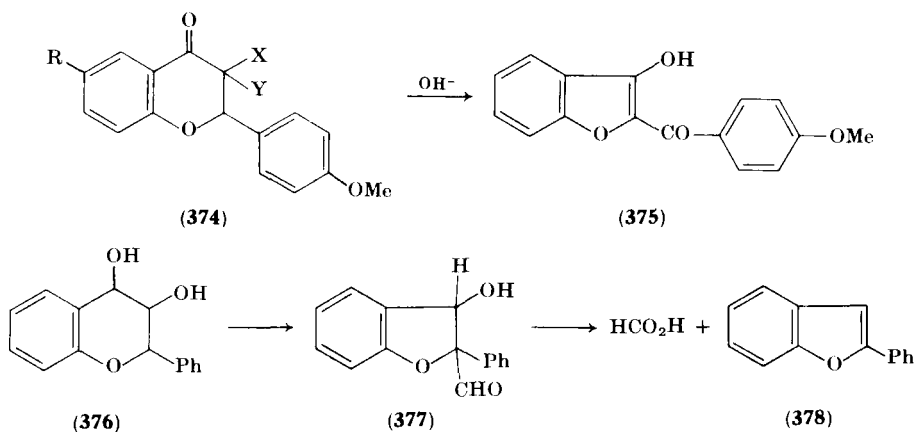
⁸²⁶ H. K. Pendse, *Rasayanam* **2**, 121 (1956); *Chem. Abstr.* **51**, 5062 (1957).

⁸²⁷ H. K. Pendse and S. D. Limaye, *Rasayanam* **2**, 107 (1956); *Chem. Abstr.* **51**, 5062 (1957).

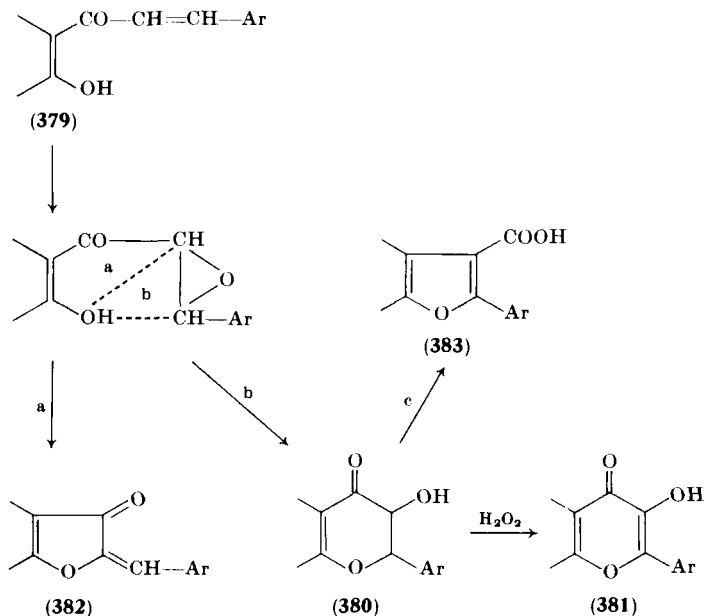
⁸²⁸ H. K. Pendse and K. S. Moghe, *Rasayanam* **2**, 114 (1956); *Chem. Abstr.* **51**, 5062 (1957).

⁸²⁹ W. Bottomley, *Chem. Ind. (London)*, 170 (1956).

⁸³⁰ M. M. Bokadia, B. R. Brown, and W. Cummings, *J. Chem. Soc.*, 3308 (1960).



The formation of 2-arylbenzofuran-3-carboxylic acids by ring closure of 2-hydroxychalcones (379) [Algar-Flynn (1934)^{831a} and Oyamada (1935)^{831b}] can be regarded as involving an intermediate flavanol. Treatment of chalcones (379) with hydrogen peroxide in an alkaline medium normally leads to flavonols (381) or to aurones (382). At the

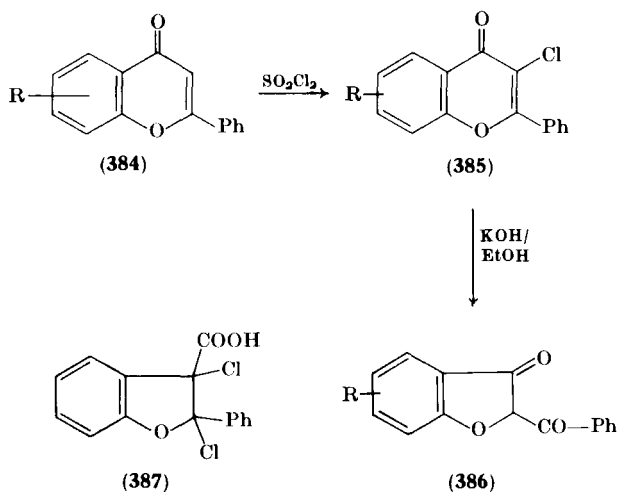


^{831a} J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad., Sect. B* **42**, 1 (1934).

^{831b} T. Oyamada, *Bull. Chem. Soc. Jap.* **10**, 182 (1935).

boiling point of the solvent the reaction leads to 2-arylbenzofuran-3-carboxylic acids with various substituents (383).^{832,833} A mechanism in several stages has been advanced, starting with dihydroflavonols (380).⁸³⁴

e. *Synthesis of Benzofurans from Flavones and Isoflavones.* 3-Chloro-flavones (385) [obtained by treatment of flavones (384, R = 6-Me or 7-OMe) with SO₂Cl₂] are hydrolyzed by KOH/EtOH to 2-benzoyl-5-methyl(or 6-methoxy)-3(2H)-benzofuranones (386).⁸³⁵ Further treatment of 3-chloroflavone by SO₂Cl₂ forms 2,3,3-trichloroflavanone, which is hydrolyzed (KOH/EtOH) to compound (387).⁸³⁶



Isoflavones (388) and dimethyloxosulfonium methylide gives 2,3-dihydro-2,3-methano-4-benzopyrones with 2-vinyl-3(2H)-benzofuranones (389) as by-products.⁸³⁷

f. *Benzofurans from α,β -Unsaturated- γ -lactones.* Reduction of an

⁸³² D. M. X. Donnelly, J. E. K. Eades, E. M. Philbin, and T. S. Wheeler, *Chem. Ind. (London)*, 1453 (1961); *Chem. Abstr.* **55**, 3435 (1962).

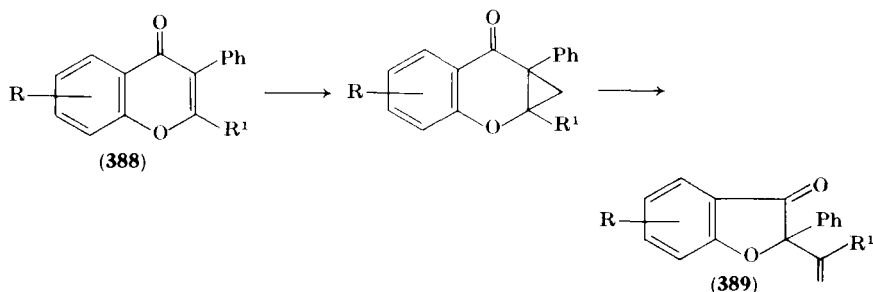
⁸³³ B. Cummins, D. M. X. Donnelly, E. M. Philbin, J. Swirski, T. S. Wheeler, and R. K. Wilson, *Chem. Ind. (London)*, 348 (1960).

⁸³⁴ B. Cummins, D. M. X. Donnelly, J. F. Eades, H. Fletcher, F. O'Cinnóide, E. M. Philbin, J. Swirski, T. S. Wheeler, and R. K. Wilson, *Tetrahedron* **19**, 499 (1963).

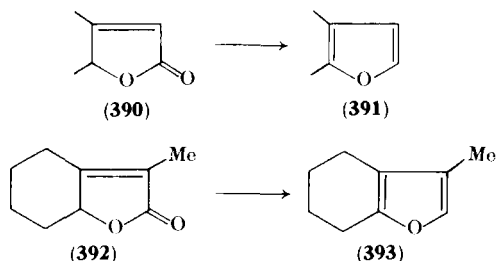
⁸³⁵ J. R. Merchant and D. V. Rege, *Tetrahedron* **27**, 4837 (1971).

⁸³⁶ J. R. Merchant and D. V. Rege, *J. Chem. Soc. D*, 380 (1970).

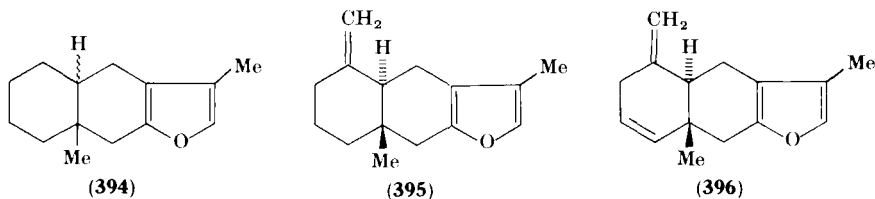
⁸³⁷ G. A. Caplin, W. D. Ollis and I. O. Sutherland, *J. Chem. Soc. C*, 2302 (1968).



α,β -unsaturated- γ -lactone (390) with an alkylaluminum hydride gives the furan ring (391).⁸³⁸



Applied to 3-methyl Δ^3 -hexahydro 2(3*H*)-benzofuranone (392) (diisobutylaluminum hydride in THF), the method leads to 3-methyl-4,5,6,7-tetrahydrobenzofuran (393),⁸³⁸ and compounds 394, 395, and 396 have been obtained by the same method from the corresponding decahydronaphthalene and octahydronaphthalene derivatives.⁸³⁸⁻⁸⁴¹



α -Acetyl- α,β -unsaturated- γ -lactones (397), rearrange on heating at 100° in HCl + AcOH to a benzofuran derivative (398).⁸⁴²

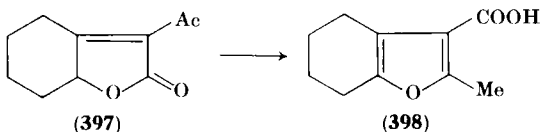
⁸³⁸ H. Minato and T. Nagasaki, *Chem. Ind. (London)* **21**, 899 (1965).

⁸³⁹ H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 377 (1966).

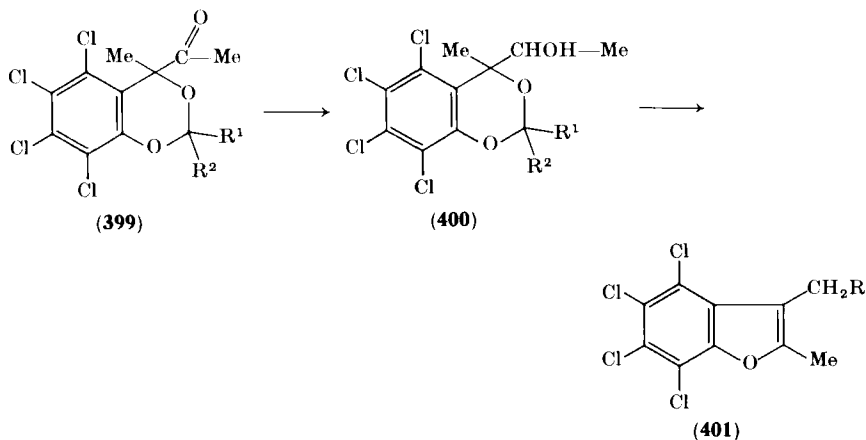
⁸⁴⁰ H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 1866 (1966).

⁸⁴¹ H. Minato and T. Nagasaki, *J. Chem. Soc. C*, 621 (1968).

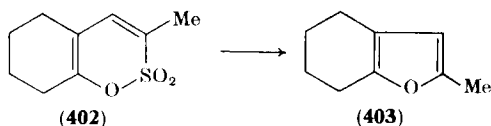
⁸⁴² R. N. Leacey, *J. Chem. Soc.*, 821 (1954).



g. *Benzofurans from Benzo-1,3-dioxans.* 4-Acetyl-2,2,4-trialkylbenzo-1,3-dioxans (**399**) are reduced (NaBH_4) to the hydroxyl derivative (**400**), which is converted ($\text{H}_2\text{SO}_4\text{-Ac}_2\text{O}$) into the benzofuran derivative (**401**, $\text{R} = \text{OAc}$). Treatment of **400** with $\text{HBr} + \text{AcOH}$ leads to **401** ($\text{R} = \text{Br}$).^{843,844}



h. *Benzofurans from δ -Sultones.* Pyrolysis, in the presence of CaO or ZnO , of sultone (**402**) leads to 2-methyl-4,5,6,7-tetrahydrobenzofuran (**403**) in 74% yield. The 2-Et (60%), 2-Ph (84%), 2,3-diMe (81%) and 3,6-diMe (75%) derivatives have also been obtained in this way.⁸⁴⁵

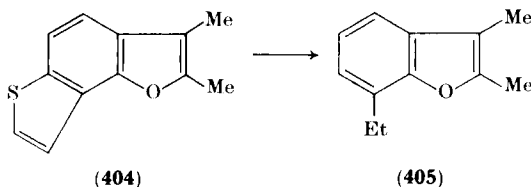


i. *Benzofurans from Thienobenzofurans.* Desulfurizing hydrogenation of thienobenzofurans (**404**) by Raney nickel leads to substituted 2,3-dihydrobenzofurans, which can be dehydrogenated to the corresponding benzofurans (**405**).^{229,856} This method makes it possible to obtain benzofurans with branched Bz-substituents.⁸⁴⁷

⁸⁴³ H. Heaney and C. T. McCarty, *Chem. Commun.*, 123 (1970).

⁸⁴⁴ H. Heaney and C. T. McCarty, *Chem. Commun.*, 124 (1970).

⁸⁴⁵ T. Morel and P. E. Verkade, *Rec. Trav. Chim.* **70**, 35 (1951).



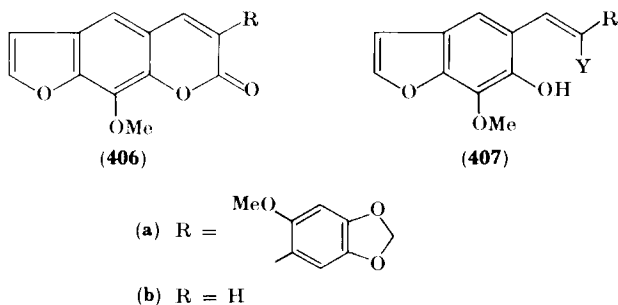
j. *Miscellaneous Methods.* Compounds with simple or fused benzofuran rings have been obtained from various compounds: hydroxyoxetans,⁸⁴⁸ monopotassium saccharate,⁸⁴⁹ indole,⁸⁵⁰ 5a,10b-dihydrobenzofuro[2,3-b]benzofuran.⁸⁵¹

3. Benzofuran Derivatives by Degradation of Natural Products

Numerous instances exist of the preparation of benzofurans (poly-substituted by more or less complex groups) of ring-opening or ring-contraction reactions of natural products.

a. *Ring-Opening Reactions.* The majority of these relate to the action of an alkali (KOH/ethanol) on 2*H*- and 4*H*-pyrone rings of complex natural products. The direct action of LiAlH_4 is also used. Other, more particular, degradations are mentioned, starting from various skeletons.

As an example, neofolin (406a), treated with LiAlH_4 , leads to the benzofuran (407a, $\text{Y} = \text{CH}_2\text{OH}$) and, with KOH/ethanol and Me_2SO_4 , to benzofuran (407a, $\text{Y} = \text{COOMe}$).⁸⁵² Other examples, are listed in Table XXII.³⁵



⁸⁴⁶ J. P. Lechartier, Thesis Univ. Paris, 1964.

⁸⁴⁷ R. Royer, P. Dermerseman, J. P. Lechartier, A. M. Laval-Jeantel, and E. Cheutin, *Bull. Soc. Chim. Fr.*, 315 (1964).

⁸⁴⁸ S. Farid and K. H. Scholz, *J. Org. Chem.* **37**, 481 (1972).

⁸⁴⁹ A. Cope and R. T. Keller, *J. Org. Chem.* **21**, 141 (1956).

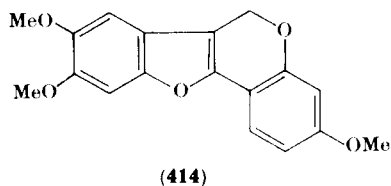
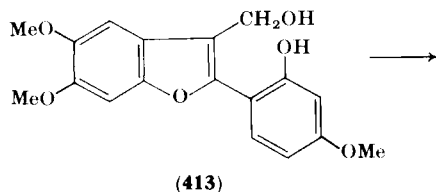
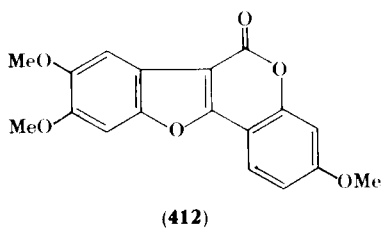
⁸⁵⁰ T. Lesiak, *Rocz. Chem.* **39**, 589 (1965).

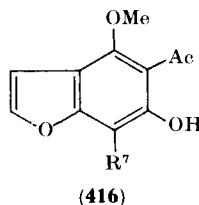
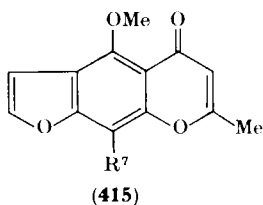
⁸⁵¹ E. Cerutti and B. Laude, *C. R. Acad. Sci.* **256**, 1122 (1963).

⁸⁵² M. Brink, W. Nel, C. J. Arall, J. C. Weitz, and K. G. R. Pachler, *J. S. African Chem. Inst.* **19**, 24 (1966); *Chem. Abstr.* **65**, 13676 (1966).

TABLE XXII
 BENZOFURANS FROM NATURAL COMPOUNDS

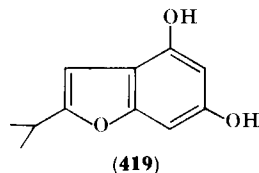
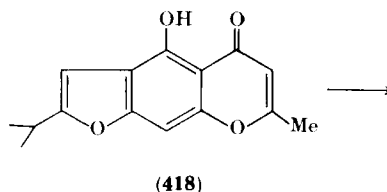
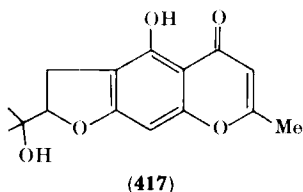
Natural compound	Benzofuran	Reagent ^a	Refer- ences
<i>Furocoumarins</i>			
Xanthotoxin (406b)	5-CH=CH—CH ₂ OH 6-OH 7-OMe	A	35
2,3-Dihydroxanthotoxin	5-CH=CH—COOH 6,7-diOMe 2,3-dihydro	B	35
Neofolin (406a)	5-CH=C(Ar)—CH ₂ OH 6-OH 7-OMe	A	852
	5-CH=C(Ar)—COOMe 6,7-diOMe	B	852
<i>Benzofurocoumarins</i>			
Wedelolactone	2-(2,4,6-TriMeOC ₆ H ₂) 3-COOH (COOMe)	B	398
	2-(2,6-OH-4-MeOC ₆ H ₂) 3-COOH 5,6-dihydroxy	B	9
	2-(2-EtO-4,6-diMeOC ₆ H ₂) 5,6-diOEt	B	9
	2-(2,4,6-TriMeOC ₆ H ₂)	B	398
	2-(2,4,6-TriMeOC ₆ H ₂) 5,6-diOMe	B	398
Coumestrol	2-(2-OH-4,5-diMeOC ₆ H ₂)	B	402
	2-(2,4-DiMeOC ₆ H ₃) 6-OMe 3-COOH	B	57
Trifoliol	2-(2,4-DiHOC ₆ H ₃) 6-OH 3-COOH	B	854
	2-(2,4-DiMeOC ₆ H ₃) 4,6-diOMe 3-COOH	B	855
	2-(2-OH-4-MeOC ₆ H ₃) 3-CH ₂ OH 5,6-diOMe	A	856

^a A = LiAlH₄, B = KOH + Me₂SO₄




Alkaline degradation of furochromones [visnagin (**415**, $R^7 = H$), khellin (**415**, $R^7 = OCH_3$)] leads to the corresponding ketones, visnaginone and khellinone (**416**).⁴⁵²

Oxidizing degradation (H_2O_2) of the same furochromones leads to the corresponding benzofuran-5-carboxylic acids.^{857,858} Similarly, alkaline degradation of **418**, a dehydration product of visamminol (**417**) (a natural coronary dilator) leads to benzofuran (**419**) and acetone.⁸⁵⁹



The action of various nucleophilic reagents causes degradation of the pyrone ring of furochromones, with the formation of benzofuran derivatives with interesting physiological properties. Thus, 4,7-dimethoxy-6-hydroxybenzofurans substituted in position 5 by a methylpyrazolyl, dimethylpyrazolyl, phenylpyrazolyl, or pyrimidyl group can be obtained⁸⁶⁰⁻⁸⁶² by the treatment of khellin (**26**) with hydrazine, methylhydrazine, phenylhydrazine, guanidinium, thiocyanate, cyanoguanidine,⁸⁶¹ or formamide.⁸⁶³ While secondary amines

⁸⁵⁷ A. Schönberg, N. Badran, and N. A. Starkovsky, *J. Amer. Chem. Soc.* **75**, 4992 (1953).

⁸⁵⁸ A. Mustafa, N. A. Starkovsky, and E. Zaki, *J. Org. Chem.* **25**, 794 (1960).

⁸⁵⁹ W. B. Benze and H. Schmid, *Experientia* **10**, 12 (1954); *Chem. Abstr.* **49**, 9638 (1955).

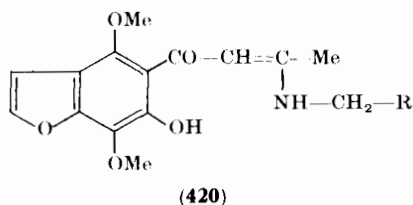
⁸⁶⁰ A. Schönberg and M. M. Sidky, *J. Amer. Chem. Soc.* **75**, 5128 (1953).

⁸⁶¹ C. Musante, and S. Fatutta, *Farmaco, Ed. Sci.* **9**, 328 (1954).

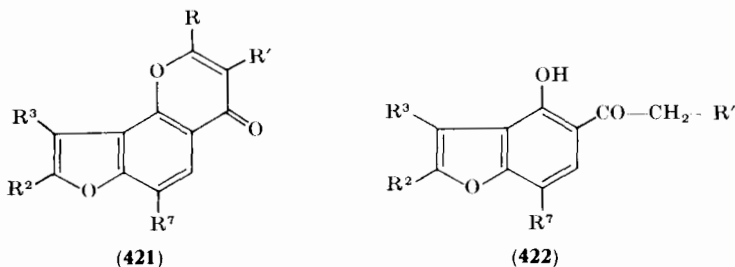
⁸⁶² C. Musante and S. Fatutta, *Ann. Chim. (Rome)* **45**, 918 (1955).

⁸⁶³ M. Hubert-Habart and R. Royer, *Chim. Ther.* **7**, 1 (1972).

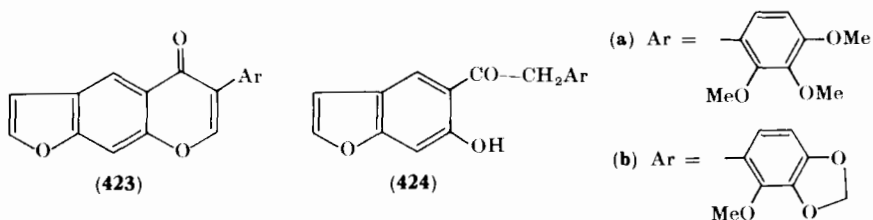
do not react, primary amines $R-CH_2-NH_2$ give compounds of the type **420**.⁸⁶⁴



Alkaline degradation (KOH/ethanol) of compounds **421** leads to 4-hydroxy-5-acylbenzofurans (**422**) and the acids $R-COOH$.⁸⁶⁵⁻⁸⁷⁰



Similarly, the isoflavone **423a**, obtained by dehydrogenation (MnO_2) of nepseudin,⁸⁷¹ leads to benzofuran (**424a**) which is oxidized (alkaline H_2O_2) to 6-hydroxybenzofuran-5-carboxylic acid. The same treatment



⁸⁶⁴ C. Musante and A. Stener, *Gazz. Chim. Ital.* **86**, 297 (1956).

⁸⁶⁵ Y. Kawase, T. Matsumoto, and K. Fukui, *Bull. Soc. Chim. Jap.* **28**, 273 (1955).

⁸⁶⁶ K. Fukui and Y. Kawase, *Bull. Soc. Chim. Jap.* **31**, 693 (1958).

⁸⁶⁷ T. Matsumoto, Y. Kawase, E. M. Nambu, and K. Fukui, *Bull. Soc. Chim. Jap.* **31**, 688 (1958).

⁸⁶⁸ R. N. Khanna and T. R. Seshadri, *Tetrahedron* **19**, 219 (1963).

⁸⁶⁹ Y. Kawase, M. Nanbu, and F. Miyoshi, *Bull. Chem. Soc. Jap.* **41**, 2676 (1968).

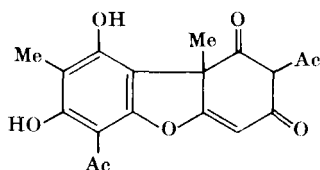
⁸⁷⁰ M. Kawazu, M. Watanabe, and E. Kaneko, Japanese Patent 71 25735 (1971); *Chem. Abstr.* **76**, 3685 (1972).

⁸⁷¹ L. Crombie and D. A. Whiting, *Chem. Ind. (London)*, 1946 (1962); *Chem. Abstr.* **58**, 9036 (1963).

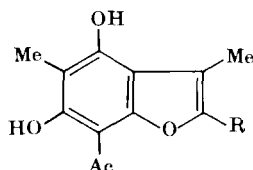
has been applied to didehydro neotenone (**424b**).⁸⁷² More complex instances are to be found in the behavior of rotenoids in alkaline medium.⁸⁷³

Thermal cracking (890°) of dibenzofuran gives 1.8% benzofuran.⁸⁷⁴

The most important natural substance with the hydrodibenzofuran structure is usnic acid (**425**), an antitubercular compound,⁸⁷⁵ several

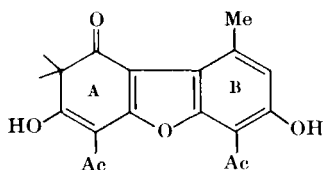


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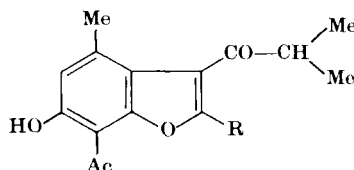


(426)

degradatory processes of which have led to benzofurans **426** ($R = CH_2-CO-CH_2-CO-Me$, $R = CH_2-COOH$, $R = Me$).⁸⁷⁶ Similarly, derivatives of usnic acid have been degraded to benzofurans or to 2(3*H*)-benzofuranones.⁸⁷⁸⁻⁸⁸⁰ Thus, benzofurans **428** are obtained on opening of ring A by ozonolysis of **427**.⁸⁷⁷



(427)



(428)

$R = COOH, H$

Oxidative degradation of the *o*-quinone (**429**), obtained by chromic acid oxidation of the corresponding benzofuran (extracted from coal

⁸⁷² L. Crombie and D. A. Whiting, *Tetrahedron Lett.*, 801 (1962).

⁸⁷³ E. S. Kondralenko and N. K. Abubakirov, *Dokl Akad. Nauk SSSR* **146**, 1340 (1962); *Chem. Abstr.* **58**, 9037 (1963).

⁸⁷⁴ C. Braekman-Danheux and A. Heyvaert, *Ann. Mines Belges*, **37** (1972); *Chem. Abstr.* **77**, 4666 (1972).

⁸⁷⁵ C. Hassal, *Experientia* **6**, 462 (1950).

⁸⁷⁶ A. M. Taha, Ph. D. Thesis, Univ. Connecticut 1966; *Diss. Abstr. B* **28**, 3666 (1968).

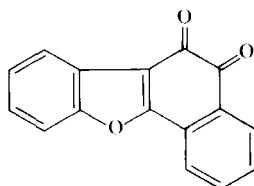
⁸⁷⁷ K. Takahashi and S. Miyashita, *Chem. Pharm. Bull.* **11**, 209 (1963); *Chem. Abstr.* **59**, 3855 (1963).

⁸⁷⁸ K. Takahashi, *Chem. Pharm. Bull.* **1**, 36 (1953).

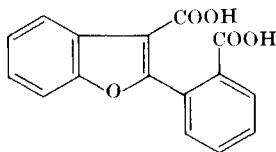
⁸⁷⁹ S. Shibata, K. Takahashi, and Y. Tanaka, *Chem. Pharm. Bull.* **4**, 61 (1956).

⁸⁸⁰ K. Takahashi and S. Shibata, *J. Pharm. Soc. Jap.* **71**, 1083 (1951).

tar), leads to the benzofuran **430**, which is decarboxylated (CaO) to 2-phenylbenzofuran.¹¹⁸

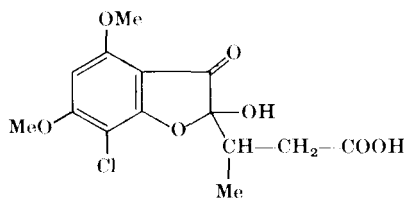


(429)



(430)

Finally, another type of ring opening is given by griseofulvin (**6**), which is degraded (KMnO₄/acetone) to the acid **431**.^{881,882}



(431)

b. *Ring Contraction Reactions*. Several benzofurans have been obtained from chroman derivatives (derived from catechin) and flavonoid compounds (derived from quercetin) through reactions that involve contraction of the oxygen-containing ring. Thus, acetolysis of the tosyl ester of tetra-*O*-methyl-(+)-catechin (**432**) gives (among other compounds) the (+)-2,3-dihydrobenzofuran derivative (**433**), which is oxidized (MnO₂) to the benzofuran **434**.^{883,884}

Quercetin (**435**), treated with sodium hydrosulfite, leads to 3(2*H*)-benzofuranone-3-one (**436**), then, through acetylation (in pyridine), to the polyacetylated benzofuran (**437**).⁸⁸⁵ Treated with KOH in water, **435** gives the 3(2*H*)-benzofuranone **438**.⁸⁸⁶ Dihydroquercetin (**439**), treated with KOH or when methylated in alkali. (KOH/MeSO₄) gives

⁸⁸¹ J. F. Grove, D. Ismay, J. McMillan, J. P. C. Mulholland, and M. A. Th. Rogers, *J. Chem. Soc.*, 3958 (1952).

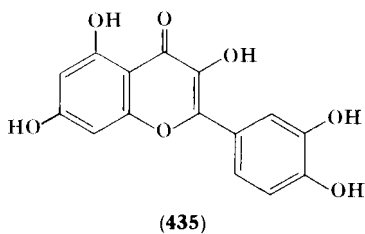
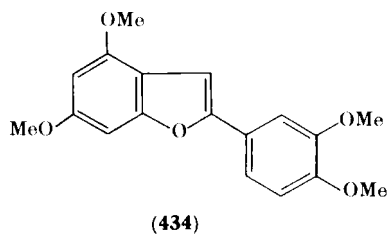
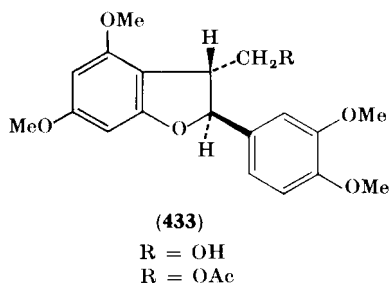
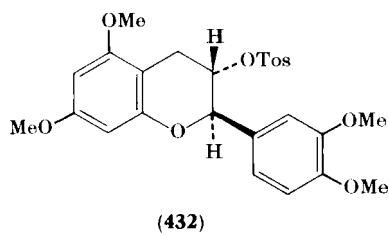
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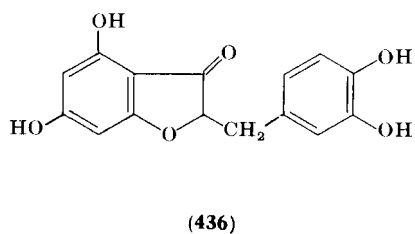
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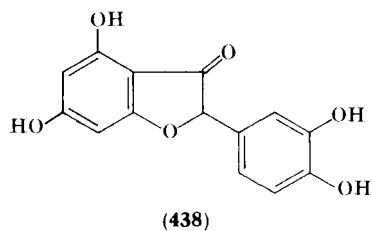
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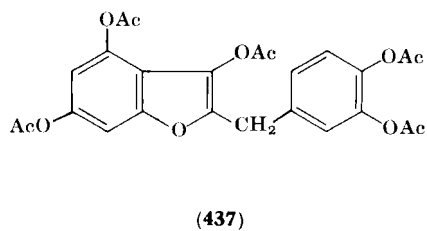
hydrosulfite



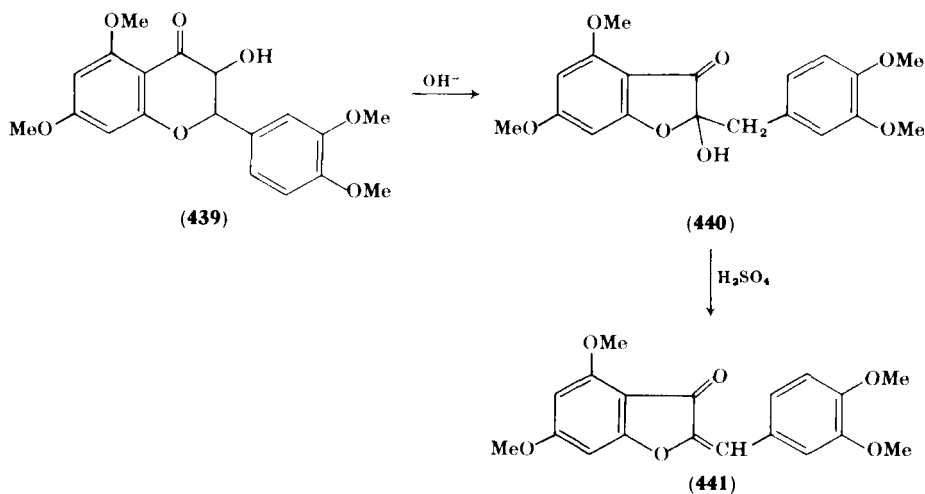
OH⁻



↓



the 2-hydroxy-3(2*H*)-benzofuranone (**440**), which is dehydrated in acidic medium to the aurone (**441**).^{147,887,888}



The 2-phenyl benzofuran and 2,3-dihydro benzofuran derivatives, which are degradation products of lignin,⁸⁸⁹ have given rise to a considerable body of research which we must consider beyond the scope of this review.

Appendix

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